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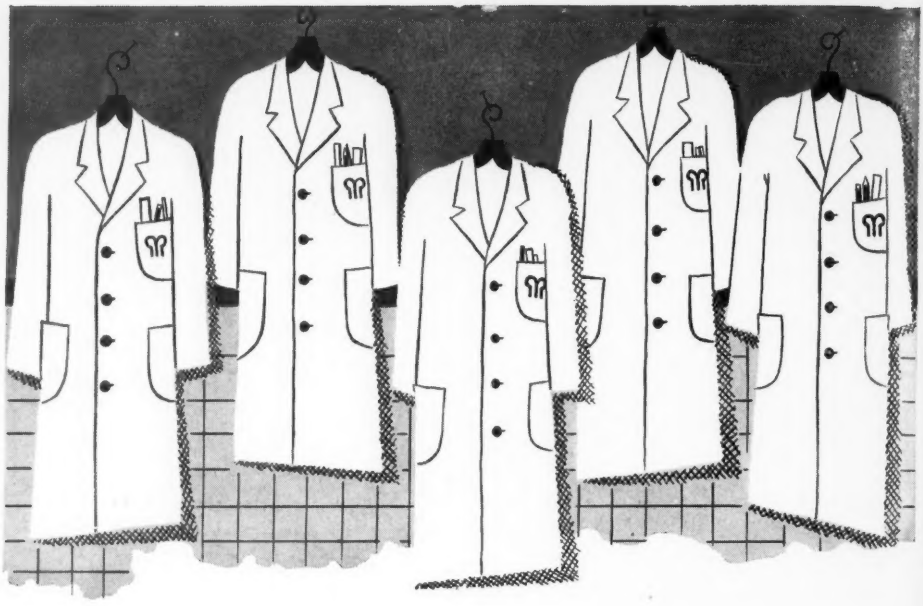

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ESTROGEN-PRODUCING SERTOLI CELL TUMORS (ANDROBLASTOMA TUBULARE LIPOIDES) OF THE HUMAN TESTIS AND OVARY. HOMOLOGOUS OVARIAN AND TESTICULAR TUMORS. III.*†

GUNNAR TEILUM, M.D.

The University Institute of Pathological Anatomy, Copenhagen, Denmark

IN PREVIOUS publications (1, 2, 3) two series of tumors (homologous) of the testis and the ovary have been established, showing complete morphological congruence in all forms of differentiation: (I) *The dysgerminoma series* (*gonocytoma*), and (II) *the androblastoma series*, forming the basis of an exact *histogenetic* classification of several special forms of tumor of the ovary, the nature and histogenesis of which have hitherto been doubtful and based on a more or less subjective judgment. This applies, for example, to the so-called mesonephroma ovarii (Schiller 1939 (4)) which displays morphological congruence with embryonal testicular tumors originating from germ cells (2) belonging to the dysgerminoma series (gonocytoma).

The virilizing so-called "adrenal tumors" and "luteoma" must also be referred to the androblastoma series, particularly on the basis of transition forms demonstrated between these and the Leydig cells in arrhenoblastomas and on the basis of morphological congruence with morphologically different types of androgen-producing interstitial cell tumors in the testis (3).

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Continued investigations into the androblastoma series which will be reported here have shown that there also occur morphologically well-defined forms of feminizing tumors, often very rich in lipoid, which because of their hormonal effect have hitherto been classified as belonging to the granulosa tumor group under the terms: folliculome lipidique (Lecène (5), Varangot (6), Plate (7)) or granulosa cell tumor of tubular or adenomatous type (Traut and Butterworth (8), Henderson (9), Dougal (10)), but which on the basis of the demonstrated congruence with androblastoma testis (Teilum 1946 (3)) can be classified with certainty as tubular androblastomas.

Several hitherto inexplicable facts concerning the hormonal effect of the testicular and ovarian androblastomas will be elucidated by these findings.

Androblastoma tubulare (lipoides) (estrogen-producing Sertoli cell tumor) of the human testis.

In my case of feminizing androblastoma testis in a man aged 53 years with gynecomastia (3) the tumor, measuring 6×4×3 cm., was found mac-

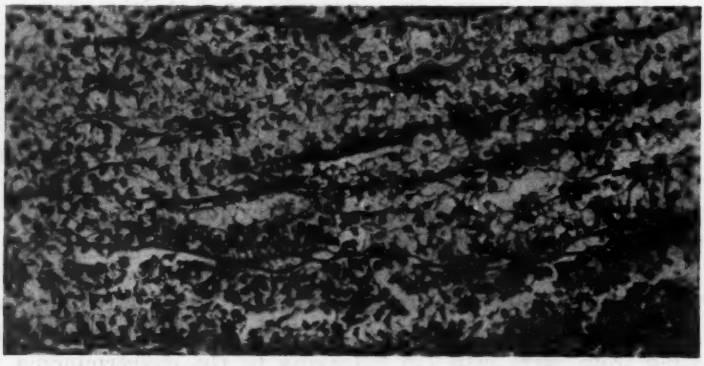

FIG. 1. Feminizing androblastoma (tubulare lipoides) testis = tubular Sertoli cell tumor, showing morphological congruence with "folliculome lipidique" (Lecène). Hematoxylin and eosin stain. ×210.

roscopically to be of an intensely yellow color on the cut surface. Posterosuperiorly a border, 4 to 5 mm. wide, of apparently normal testicular tissue was found. The *histological* examination showed a motley picture corresponding to the various stages of differentiation in virilizing arrhenoblastomas of the ovary, with all transitions from a diffuse blastema to differentiated massive cords and tubuli. In the greater part of the tumor the tubuli were highly differentiated with bright cylindrical cells, characterized by a very copious content of lipoid, so that the tumor tissue in

these portions presented the histological picture of a tubular lipoid cell tumor. The tissue, in the parts where the trabeculae had been cut parallel to their longitudinal axis, was seen to consist of two rows of cylindrical cells with highly vacuolated cytoplasm (Figs. 1 and 3), whereas the trabeculae, when cut at right angles with their longitudinal axis, displayed a radial arrangement of the cells (Fig. 4) with transition to tubular cavities with cylindrical or cubical cells in a layer circumscribing a central cavity. A considerable lipoid content was demonstrated by means of osmium and sudan staining (Fig. 2).

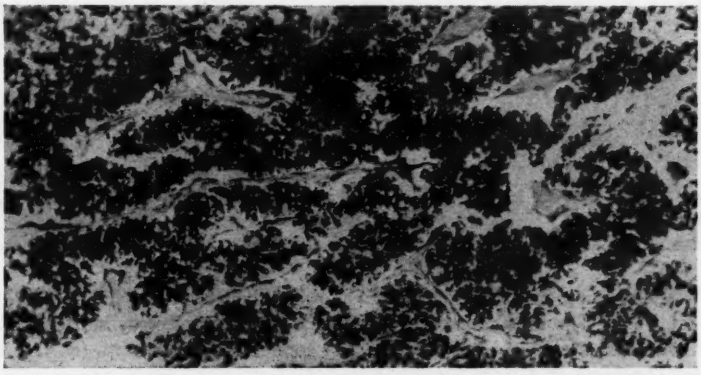

FIG. 2. Feminizing androblastoma of human testis (osmic acid stain). The tubuli consist of Sertoli cells with considerable lipid content (*cf.* Huggins & Moulder's figure 5 showing tubular Sertoli cell tumor of canine testis). ×240.

Androblastoma tubulare (lipoides) (estrogen-producing Sertoli cell tumor) of the human ovary, hitherto considered as "folliculome lipidique" (Lecène) or as "granulosa cell tumor of tubular or adenomatous type" (Table 1).

a) *Three cases of "folliculome lipidique" (Lecène, Plate), collected by Varangot in 1937*

As previously described ((3), figs. 9 and 10 *a* and *b*), the lipidic tubular portions of the tumor of the testis were found in all respects to be identical with the so-called "folliculome lipidique" of the ovary of which Varangot in his monograph on granulosa cell tumors (1937, pages 140 to 151 (11)) gave a detailed description with eleven photomicrographs. This study was based on the 3 cases known till then, namely 2 cases observed by Lecène and the third by Plate. The first case, observed as early as 1910, was examined histologically by Lecène and presented by Christian before the

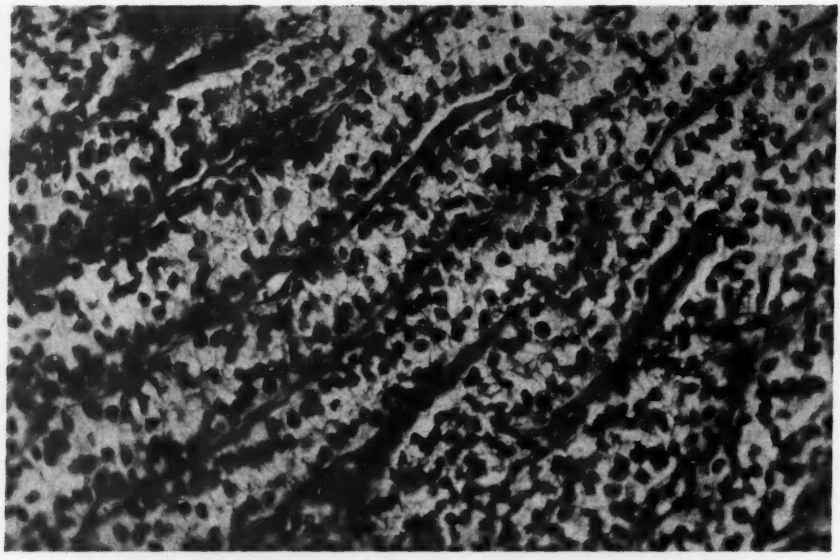

FIG. 3. Feminizing androblastoma testis showing the trabeculae cut parallel to their longitudinal axis. The linear bands of cells contain two rows of cylindrical cells with highly vacuolated cytoplasm and separated by connective tissue septa (*cf.* "folliculome lipidique" (Lecène)). v. Gieson-Hansen stain. ×370.

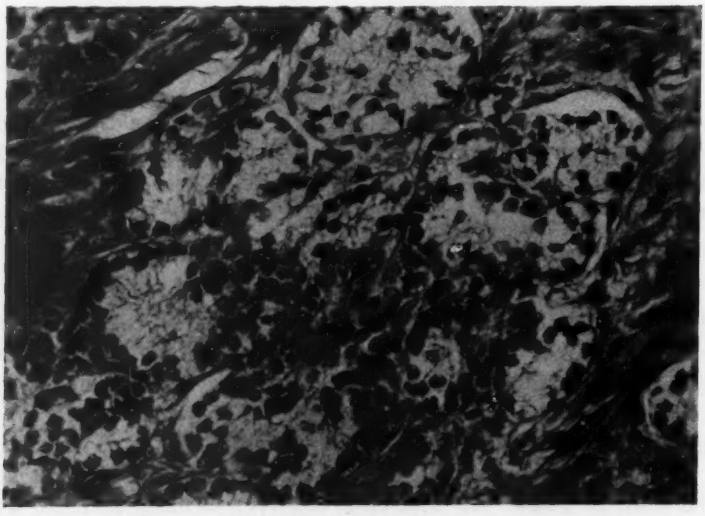

FIG. 4. The same testicular tumor. The trabeculae cut at right angles with their longitudinal axis. Radiate arrangement of the lipidic, highly vacuolated cells (*cf.* Henderson's figures 2 D and 10 B, "luteoma of adenomatous type"). v. Gieson-Hansen stain. ×310.

Société anatomique (12). Lecène observed another case in 1927, and Plate found the third in 1933.

The fact that, macroscopically, the tumor is of a yellow color indicates a high content of lipoid. Varangot described the ovarian tumor histologically

TABLE 1. TEN CASES OF ANDROBLASTOMA TUBULARE LIPOIDES OVARII OR TUBULAR SERTOLI CELL TUMOR

Author	Earlier diagnosis	Patient's age (yrs.)	Endocrine symptoms
1. Christian = Lecène I (1910)	Folliculome lipidique	21	Metrorrhagia
2. Lecène II (1927)	Folliculome lipidque	—	
3. Plate (1933)	Folliculome lipidique	23	Metrorrhagia, hyperplasia endometrii; later amenorrhea 7 months
4. Traut & Butterworth I (1937)	Tubular granulosa cell tumor	—	Not stated
5. Traut & Butterworth II (1937)	Folliculome lipidique	—	—
6. Henderson (1942)	Luteoma of adenomatous type	7	Metrorrhagia and pubertas praecox
7. Dougal (1945)	Granulosa cell tumor of tubular or adenomatous type	22	Metrorrhagia
8. Grevle (1936)	Granulosa cell tumor of special structure	26	Metrorrhagia
9. Pick (1905)	Adenoma tubulare	34	Metrorrhagia
10. Schickele (1907)	Adenoma tubulare	26	Metrorrhagia

as composed of "des bandes cellulaires tantôt rectilignes, tantôt flexueuses et festonnées, separées par des travées conjonctives le plus souvent fines et lâches, parfois hyalinisées."

The characteristic pictures, dependent on whether the trabeculae are cut parallel or at right angles to their longitudinal axis, are identical with those described in the section on testicular androblastoma.

The cells seem to be distended by their cytoplasmic content and with sudan-staining they are seen to be filled with sudanophilic drops. The distribution of lipoid is not absolutely uniform and both in the ovarian tumor and in the corresponding testicular tumor, zones can be observed in which it is less copious. Lecène considered this accumulation of fat as being indicative of a luteinization. Plate agreed with Lecène and considered the hormonal function of the tumor tissue to be identical with that of the corpus luteum. Varangot, on the other hand, justly pointed out that accumulation of lipoid and luteinization are not synonymous. The cells have absorbed fat, but they are not of the same appearance as lutein cells. Functionally, no signs of lutein effect were found in these cases either. No signs of lutein influence were demonstrated either in Lecène's or in Plate's cases upon examination of the endometrium. Plate stated that the endometrium was hyperplastic. Varangot found that the hyperplasia suggested a folliculin-producing tumor. In the identification of the growth as a granulosa cell tumor he attributed greater importance to this functional test than to the morphological conditions, which, with regard to the occurrence of cylindrical cells, tubular and adenomatous structures, display such considerable and inexplicable deviations from the ordinary structure of the granulosa cell tumors.

b) *Two cases described by Traut and Butterworth (1937)*

In Traut and Butterworth's paper (8) photomicrographs are reproduced showing two ovarian tumors of the same type. In their figure 3 *b*, the structure is described as "tubular arrangement which is quite rare. Unquestionably granulosa, but simulating Pick's tubular adenoma," and their figure 4 *b* is labelled "general type of Lecène-folliculome lipidique."

Traut and Butterworth point out that there is no biological proof of progesterone effect of this so-called "folliculome lipidique," and they say as follows about the "tubular granulosa cell tumour": "Rarely the granulosa cells form a system of tubules in which single rows of cells arrange themselves about a central acinus as though it were a duct. Such an arrangement of cells might be thought to be related to some form of tubular adenoma, such as Pick's testicular tumor, were it not that one can usually prove beyond doubt that they are true granulosa cells."

c) *Henderson's case of "granulosa cell tumor of adenomatous type" (1942)*

Henderson's series (9) of 21 granulosa cell tumors and 9 theca cell tumors includes one case of "granulosa cell tumor of an adenomatous type" which is termed rare. The photomicrographs with cross-sections of bright tubuli with epithelial cells rich in lipoid (their figures 2 D and 10 B) are identical with our testicular androblastoma (*see* Fig. 4). Henderson's case was that

of a 7-year-old girl with vaginal hemorrhage and pubertas praecox. The tumor was 4 cm. in diameter. The patient was alive and well six years after the operation. The endometrium had not been examined. The tumor was also termed "luteoma, adenomatous type" and was considered "completely luteinized," as the copious lipoid content was considered synonymous with luteinization in spite of the marked clinical signs of an estrogenic effect of the tumor.

d) *Dougal's case of "granulosa cell tumor of tubular or adenomatous type" (1945)*

A particularly instructive and thoroughly described case of this form of tumor of the ovary is the one reported by Dougal (10) in a 22-year-old woman with persistent uterine hemorrhage of seventeen months' standing. The diagnosis of granulosa cell tumor was established. At operation a solid, almost spherical, ovarian tumor, measuring 7.5 cm. in diameter, was removed. On the cut surface it was seen to be encapsulated, somewhat lobulated and of *a bright yellow color*. The histological picture was found to be "quite different" from the one usually found in granulosa cell tumors, as "the tumor was seen to consist of an encapsuled mass of perfectly formed tubules more or less divided up into lobules by incomplete septa, well supplied with blood-vessels. Lying over part of the circumference of the tumor and outside the capsule were the remains of the ovary proper containing Graafian follicles in various stages of development, a number of corpora albicantia but no recent corpora lutea. The general arrangement of tumor and ovary suggested that the tumor had not originated in the ovarian cortex, but in the medulla or hilum.

Microscopically the tubules were seen to be fully differentiated and to consist of a single layer of cylindrical cells with well marked inner boundaries and oval, deeply staining, peripherally placed nuclei. Sudan III stain revealed the presence of large amounts of lipid in the inner portions of the cells and in the lumina." Dougal considered the tumor to be an encapsulated, luteinized and hormonally active adenoma of the ovary. According to the clinical history the hormonal effect seems to have been *estrogenic*. The tumor was stated to be highly differentiated "but along unusual lines, the tubular arrangement being not unlike that present in Pick's testicular adenoma of the ovary which, however, is a virilizing tumor." The colored plates reproduced in Dougal's paper show complete conformity with similar sections in my case of feminizing androblastoma testis (Figs. 2 and 4).

e) *Grevle's case 2 of granulosa cell tumor of peculiar character*

Grevle's case (13) in a 26-year-old woman with metrorrhagia is of the same type. At the site of the right ovary a solid tumor was found at oper-

ation, being approximately the size of a chicken's egg and very easily enucleated, so that only a narrow border of ovarian tissue remained. On the cut surface the tumor was of a yellow color and of a rather soft consistency. Microscopically it was composed of cells arranged in gland-like or tubular formations. The epithelium was almost cylindrical. After operation the menstrual periods became regular. It appears from the photomicrographs reproduced that the tumor was of the same type as in the preceding cases, but less lipidic than "folliculome lipidique" Lecène.

Morphological congruence and common estrogenic effect of androblastoma lipoides of the testis and the ovary (Table 2).

Eight cases of tubular or adenomatous, most frequently highly lipidic,

TABLE 2. RELATION BETWEEN DOMINANT CELL TYPE AND HORMONAL EFFECT IN IDENTICAL ANDROBLASTOMAS OF THE TESTIS AND THE OVARY

	Testis	Ovary
I. Estrogen-producing androblastoma:—Androblastoma tubulare lipoides = Sertoli cell tumors		
Structure	chiefly tubular, lipidic	
Hormone production	estrogen	estrogen
Endocrine effect	feminizing; gynecomastia, impotence	feminizing; metrorrhagia, in children also pubertas praecox (Henderson)
Cases described	in man (Teilum, 1945–1946) in dog (Huggins & Moulder, 1945)	a number of tubular lipidic tumors, previously misinterpreted as folliculome lipidique (Lecène) or tubular granulosa cell tumor, and the pure tubular adenoma (see Table 1)
II. Androgen-producing androblastoma (besides Robert Meyer's virilizing arrhenoblastomas):—Androblastoma diffusum = Leydig cell tumors		
Structure	diffuse, often lipidic	
Hormone production	androgen	androgen
Endocrine effect	in adults: none in children: pubertas praecox	in adults: virilization in children: also pubertas praecox
Cases described	Masson's case and several others	tumors described as "adrenal tumors" and "luteomas"

ovarian tumors which, macroscopically, are yellow on the cut surface have thus been collected from the literature where they have hitherto been described as "folliculome lipidique" (5, 6, 7, 8, 11, 14) "completely luteinized" granulosa cell tumor (9) or granulosa cell tumor of tubular or adenomatous type (luteinized and hormonally active adenoma) (10).

On the basis of the demonstrated morphological congruence with the feminizing androblastoma testis (3) these tumors can with certainty be histogenetically classified as *androblastomas, i.e.,* tumors which, like the virilizing arrhenoblastomas, originate from a testicular blastema (androblastema) in which a differentiation tending in the direction of Sertoli and (or) Leydig cells may take place, the hormonal effect of the tumor thus being dependent on predominance of either type of cell. The purely or chiefly tubular lipidic forms, like those dealt with here, will in principle correspond to the lipidic estrogen-producing tubular Sertoli cell tumors of the testis described in dogs (Huggins and Moulder (15)), as we may take it for granted that the lipidic cells in the tubular sections of the androblastomas represent Sertoli cells.

In the ovary, too, these tumors are hormone-producing. Although most of the cases have been looked upon as "folliculome lipidique" (Lecène) or as luteinized granulosa cell tumors of tubular type, no biological proof of progesterone effect of this form of tumor has been delivered (6, 8, 11). The clinical details such as metrorrhagia and, in Henderson's case in a 7-year-old girl, also pubertas praecox, and observations of endometrial hyperplasia in a few cases, indicate an active estrogen-production of the tumor (6). This form of tumor is highly differentiated and has proved to be benign in all the cases described. Several of the authors of the case reports emphasize the morphological resemblance to tubular adenoma of the ovary (7, 8, 10), but they all interpret the tumors as belonging to the granulosa cell tumors, as apparently they have attributed a greater importance to the function of the tumor than to the morphological conditions which, as pointed out by Varangot, display such considerable deviations from the ordinary structure of the granulosa cells.

It may be mentioned that during recent years the term "folliculome lipidique" has been used as a synonym for any luteinized granulosa cell tumor (Novak (16)), but that the papers reported here deal only with tubular tumors identical with Lecène's original type.

Macroscopically the tubular androblastomas are not very large. They are often of almost spherical shape, solid, of a yellow color on the cut surface and well encapsulated in many cases, with a border of ovarian tissue surrounding the tumor.

Histologically, more or less lipidic tubuli with bright vacuolated cylindrical cells are seen; where the trabeculae have been cut parallel to their

longitudinal axis the cells form long parallel bands with two rows of cells (Figs. 1 and 3), whereas in cross-sections a radial arrangement of the cells is seen (Fig. 4), often surrounding a distinct lumen.

Histogenesis and classification. The histogenetic classification of the tumor as a chiefly *tubular androblastoma* is based upon

1. *The morphological congruence* between "folliculome lipidique" of the ovary and the predominant sections of the feminizing androblastoma testis ((3), fig. 9 *a* and *b*), and

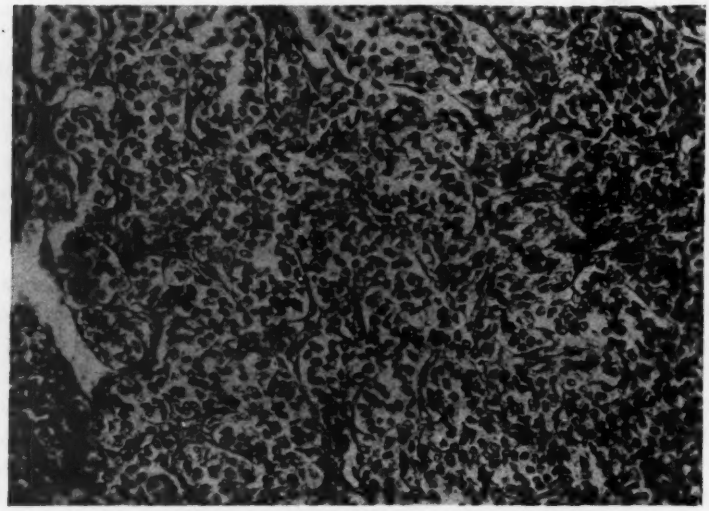

FIG. 5. Solid cords of undifferentiated Sertoli cells of androblastoma testis (*cf.* Figures 6 and 7). v. Gieson-Hansen stain. ×240.

2. *the gradual transition* from solid cords and tubuli, which may be found in virilizing ovarian arrhenoblastomas (Fig. 6) as well as in the homologous testicular androblastomas (Fig. 5), to the highly differentiated lipidic tubuli with vacuolated cells (Figs. 1 and 3).

Thus there cannot be any doubt that the group of lipidic tubular ovarian tumors dealt with here and previously described as "folliculome lipidique" (Lecène's type) or granulosa cell tumor of tubular or adenomatous type—irrespective of their estrogenic effect—does not belong to the group of granulosa cell tumors, but represents ovarian tumors congruent with androblastoma tubulare (lipoides) of the testis (3) and must be classified as *androblastomas, i.e.*, tumors which, like the arrhenoblastomas, originate histogenetically from male directed cell material.

Nature of the hormone-producing cells of androblastomas.

At first glance such an interpretation of these *estrogen*-producing ovarian tumors as tumors originating from a *testicular* blastema or *male* directed cell material may perhaps seem difficult to explain. In this connection, mention should be made of Huggins and Moulder's demonstration of estrogen production of highly lipidic, often tubular, Sertoli cell tumors of the testis in the dog (15).

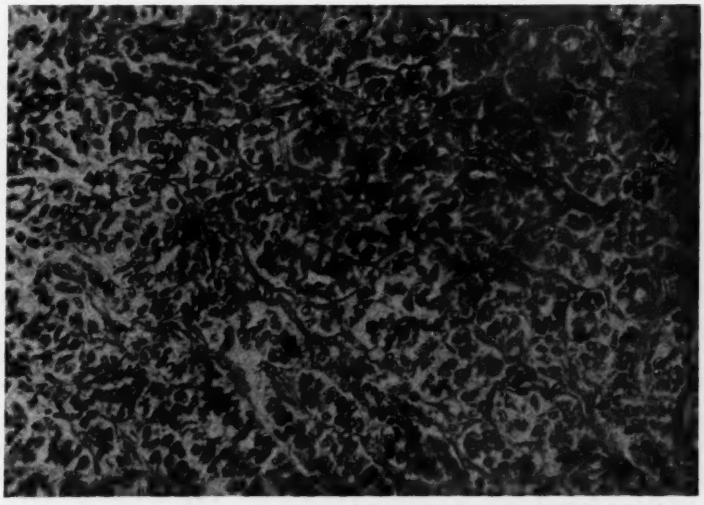

FIG. 6. Solid cords of undifferentiated Sertoli cells of virilizing arrhenoblastoma ovarii (*cf.* Figures 5 and 7). v. Gieson-Hansen stain. ×240.

In 1918 Sand (17) advanced, with his vicario-theory, the view that under certain conditions the Sertoli cells take part in the hormone production of the testis.

In 1942 Klinefelter, Reifenstein and Albright (18) described a clinical syndrome (so-called Klinefelter syndrome) characterized by bilateral gynecomastia, aspermatogenesis without absence of Leydig cells, increased secretion of F.S.H. and hyalinization of the tubuli, so that both germinal cells and Sertoli cells were involved. These authors supposed that in addition to androgenic hormone from the Leydig cells the testis also produced another hormone similar to estrin from the tubuli, and they also pointed out that inhibition of formation of castration cells is not a physiological function of testosterone. In conformity therewith the syndrome described by Castillo, Trabucco and Balze (19) shows absence of germinal epithelium

without impairment of the Sertoli or Leydig cells, whereas the secretion of F.S.H. is normal. This is taken as a sign that the Sertoli cells regulate the gonadotropic activity of the pituitary by means of a secretion product.

Testis tumors with estrogen effects have often been described in dogs (lit., *see* (15)). The dogs are sexually attractive to other males, the mammary glands are enlarged, with hypertrophy of the mammary papillae. Squamous metaplasia of the epithelium of the prostate and posterior urethra is usual. The site of estrogen production had not been identified before the work of Huggins and Moulder (15) in 1945. They say as follows about this question: The germinal epithelium of the gland is certainly not its source, as the tumors derived from the germinal epithelium (seminomas) do not cause squamous metaplasia of the prostate. That the Leydig cells should produce estrogenic hormone does not fit in with cases where interstitial cell neoplasms produce large amounts of the male sex hormones. An adult described by Masson (1943 (20)) with a malignant interstitial cell tumor had an extremely large titer of urinary androgen but no gynecomastia.

The hypothesis that these tumors of the canine testis are derived from Sertoli cells is based by Huggins and Moulder on histochemical study of the lipoids and estrogen extraction and assay. It appeared that all testis tumors of feminized dogs contained large amounts of lipoid—from 75 to 370 per cent more than normal canine testis. In 3 cases the neoplastic cells were arranged in tubular formation, and in 2 others abortive tubular formation was present. By definition, the cells of the testicular tubules with high lipid content are Sertoli cells. The estrogen content of these lipidic neoplasms was found to be considerable; in one of Huggins and Moulder's cases it was equivalent to 0.07 mg. per Kg. calculated as α-estradiol benzoate, "being twice the content of the ovaries at estrus and one-third of the amount in equine testis, the richest known source of estrogen." Estrogen could not be extracted from a Sertoli cell tumor that had not caused feminization.

When a morphological comparison is made between the Sertoli cell tumors in dogs and the feminizing and chiefly tubular androblastoma testis in man (Figs. 1 to 5) there can, in spite of all differences (*e.g.*, with regard to the degree of differentiation of the cells), be no doubt that the cord-shaped and tubular portions of the androblastomas are identical in principle with the structure of the Sertoli cell tumors in dogs, just as the cells of the cords and tubuli of arrhenoblastomas must be considered identical with the Sertoli cells of the testis. The considerable lipoid content of the cells in the highly differentiated tubular portions also shows complete conformity (compare our Fig. 2 with Huggins and Moulder's fig. 5).

Cases of Sertoli cell tumors in dogs, with closely set solid cords without

distinct adenomatous structure (Fig. 7) are morphologically identical with corresponding parts of arrhenoblastoma ovarii (Fig. 6) and androblastoma testis (Fig. 5).

Thus tumors of the androblastoma series (including the arrhenoblastomas) may contain two different types of hormone-producing cells corresponding to Leydig cells and Sertoli cells (or their precursory stages) with production of androgenic and estrogenic hormones respectively (Fig. 8).

A testicular tumor with complete dominance of Leydig cells and production of androgenic hormone will give an increased output of this hor-

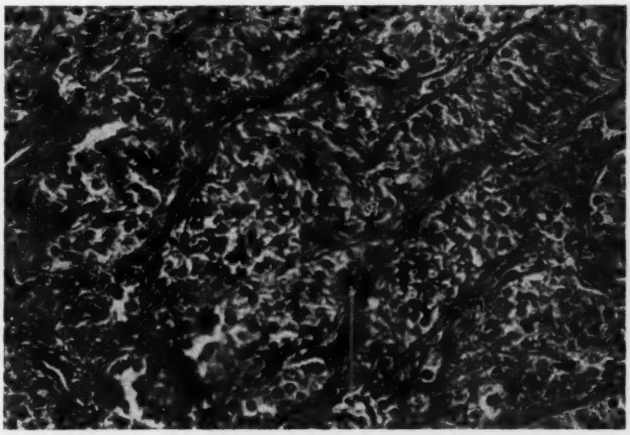

FIG. 7. Solid cords of Sertoli cells in Sertoli cell tumor of canine testis. (*cf.* tumors of human testis (Fig. 5) and of human ovary (Fig. 6)). Hematoxylin and eosin stain. ×240.

mone (as in Masson's case), but no clinical symptoms of endocrine disease. In the ovary, on the other hand, the homologous tumor will be clinically virilizing and correspond to tumors which have previously been incorrectly described as adrenal cell tumors or luteomas, but which are actually diffuse androblastomas homologous to Leydig cell tumors (Teilum (3)).

The virilizing effect of arrhenoblastomas of intermediary or diffuse type will also be dependent on occurrence and dominance of hormonally active Leydig cells or their precursory stages.

It has long been a well-known but inexplicable fact that the most highly differentiated arrhenoblastomas, by which has been understood the purely or chiefly tubular forms, most frequently have little or no hormonal (*i.e.* virilizing) effect. This is, however, quite simply explained by the occurrence of those types of cell in which the production of androgenic or estrogenic hormone respectively is possible. If the tumor tissue contains chiefly,

or exclusively, tubular parts (containing Sertoli cells), the androgenic effect will fail to appear.

Ovarian tumors with dominance of tubular portions and a simultaneous marked accumulation of lipoid in their epithelium—similar to what is found in the most highly hormonally active Sertoli cell tumors in dogs—must then in advance be expected to exert an estrogenic effect.

This is just what we find in the cases referred to in the preceding pages—cases of tubular ovarian tumors with a high lipid content (metrorrhagia, pubertas praecox) which, however, has caused them to be misinterpreted

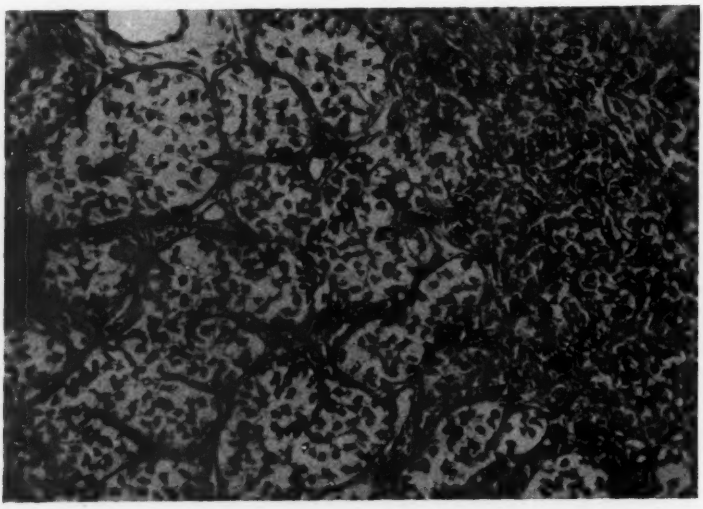

FIG. 8. Androblastoma testis. Differentiation of cords containing Sertoli cells in diffuse androblastoma. v. Gieson-Hansen stain. ×240.

as granulosa cell tumors (folliculome lipidique (Lecène), granulosa cell tumor of tubular or adenomatous type), in spite of the fact that the morphological structure differs from the usual one characteristic of tumors of the granulosa cell group. The histological structure, on the other hand, is completely identical with that of androblastoma testis (Figs. 3 and 4).

In other words, owing to the occurrence of both androgen-producing Leydig cells and estrogen-producing Sertoli cells in the testicular androblastomas we can also expect to find both androgen- and estrogen-producing tumors in the series of homologous ovarian androblastomas.

This throws light on still another phenomenon which seemed previously inexplicable (Pedersen (21)), namely, that the androblastomas appear to be virilizing in women but feminizing in men.

This is simply due to the fact that only androblastomas with preponderance of estrogen-producing Sertoli cells give rise to clinical symptoms of endocrine disease in males, whereas the corresponding tumor of the ovary may be either virilizing (in case of dominance of Leydig cells) or feminizing—just like the testicular tumor (in case of dominance of Sertoli cells). As demonstrated above, it has, however, in the latter case been misinterpreted as "folliculome lipidique" or tubular granulosa cell tumor. As will be seen, only the heterologous hormonal effect has been recognized clinically.

According to these findings it was to be expected that pure, so-called "tubular adenomas" of the ovary are not only clinically without any virilizing effect, which, as already mentioned, is well-known, but would be found in a number of cases to be estrogen-producing, like granulosa cell tumors; and, again like these, associated with metrorrhagia in some cases. An examination of the literature on the subject proves that this is so. Both the case described by Pick (1905 (22)) and the one reported by Schickele (1907 (23)), both cases of tubular adenoma, had marked uterine hemorrhage in the anamnesis, a hitherto completely unnoticed and also inexplicable symptom in tubular adenoma.

In this connection mention may also be made of a case (reported by Goldberg and Maxwell (1947 (24)) of bilateral arrhenoblastoma without masculinization in a 19-year-old girl presenting a paradoxical picture of primary amenorrhea, tall eunuchoid build, large breasts, poorly developed external genitalia with rudimentary vagina, congenital absence of uterus and cervix, absent axillary and scant pubic hair and a high gonadotropin titer. Operation revealed bilateral, poorly developed gonadal structures composed of tissue grossly resembling adrenal cortex, proved to be a highly differentiated type of arrhenoblastoma. Careful search revealed no evidence of ovarian tissue. It is added that "the source of the estrogens responsible for the breast development remains a mystery."

The ovarian tumors are identical with the estrogen-producing androblastoma tubulare lipoides and in all probability responsible for the breast development.

The high lipid content in the tubular hormone-producing androblastomas in man and dog is in good conformity with Greenblatt, Greenhill and Brown's (1939 (25)) demonstration of the fact that incretory tumors differ from the nonincretory tumors in that the former have a consistently greater phospholipid and cholesterol content than the latter.

According to what has been set forth in the preceding pages, it is incorrect to consider the tubular androblastoma as the only highly differentiated form. The nontubular portions of the androblastomas may contain equally differentiated cells, namely Leydig cells, but with a qualitatively

different hormonal production. The feminizing tubular lipid-cell tumor and the virilizing Leydig cell tumor (mistaken in the ovary for "adrenal tumor," "luteoma") both represent highly differentiated, hormone-producing androblastomas with dominance of Sertoli cells or Leydig cells respectively. In the undifferentiated diffuse forms (so-called sarcomatous type) it is, as a rule, impossible to decide whether the cell type represents mother cells of Sertoli or of Leydig cells. In a case such as the one reported by Østergaard (26)—chiefly diffuse feminizing testicular tumor, described as "presumably aberrant adreno-cortical tumour"—a radiating arrangement in parts forming small alveoli could, however, in addition to the cytological findings, indicate that this was a case of undifferentiated Sertoli cell tumor.

Terminology.

The term *androblastoma* (androma) was introduced by me to designate a series of tumors in the testis, homologous (and morphologically congruent) with the arrhenoblastoma series defined by Robert Meyer (27). As these tumors of the testis were not virilizing, the term arrhenoblastoma could obviously not be applied to them. Continued examinations of homologous tumors (3) showed, however, that Robert Meyer's group had to be extended so as to comprise also the diffuse so-called "adrenal cell tumors" (= Leydig cell tumors) with virilizing effect and the so-called "folliculome lipidique" (Lecène, Plate) with estrogenic effect, as they both displayed morphological congruence with the testicular androblastomas. Thus the histogenetically defined series of tumors also comprises types of tumor in the ovary which, in spite of their origin from male directed material, are not only without any virilizing effect but, in the case of the purely tubular forms, are estrogenic. It seems to me to be consistent to term the whole of this group of tumors androblastomas—of the ovary as well as of the testis—and to leave Robert Meyer's term arrhenoblastoma for the group which is, in addition, characterized clinically as virilizing.

As far as the highly differentiated pure, or chiefly pure, forms mentioned in the preceding pages are concerned, the terms tubular Sertoli cell tumor (15) or ovarian Leydig cell tumor may be employed, but to illustrate the histogenesis and the continuity between the individual forms of differentiation in the testis and the ovary the term androblastoma seems to be adequate.

SUMMARY

1. In continuation of previous studies on identical tumors of the ovary and the testis a morphological congruence is demonstrated between the feminizing androblastoma (tubulare lipoides) testis and feminizing

ovarian tumors, which have previously been described as "folliculome lipidique" or granulosa cell tumors of tubular or adenomatous type.

2. These ovarian tumors can thus be classified as androblastomas, *i.e.*, tumors originating from a testicular blastema in which a differentiation tending in the direction of Sertoli and (or) Leydig cells may take place.

3. The estrogenic effect of androblastoma tubulare lipoides of the human ovary as well as of the testis is explained by dominance of tubular portions (Sertoli cells) in accordance with Huggins and Moulder's demonstration of estrogen-producing, lipidic (often tubular) Sertoli cell tumors in dogs. Similarly, the hormonal effect of virilizing androblastomas, *i.e.*, arrhenoblastomas and Leydig cell tumors (so-called "adrenal cell tumors" and "luteomas"), is supposed to depend on a dominance of androgen-producing Leydig cells.

4. Through the histogenetical classification of the androblastomas the following, hitherto inexplicable, points are elucidated:

a) That the "most highly differentiated" (*i.e.*, chiefly tubular) arrhenoblastomas have the least pronounced (frequently lacking) hormonal (*i.e.* virilizing) effect.

b) The apparently different hormonal effect of the androblastomas in either sex (feminizing in males, virilizing in females).

c) The hitherto unnoticed condition that the purely tubular testicular adenoma of the ovary is often associated with metrorrhagia.

d) The estrogen effect (development of the breasts) in cases of bilateral, yellow, purely tubular "arrhenoblastomas" with simultaneous aplasia of the genital system, including the ovaries.

REFERENCES

1. Teilum, G.: Feminizing testicular tumor with the same structure as arrhenoblastoma of the ovary (in Danish, with English summary), *Nord. med.* **27**: 1965–1968 (Sept.) 1945.
2. Teilum, G.: Gonocytoma. Homologous ovarian and testicular tumors I. With discussion of "mesonephroma ovarii" Schiller, *Acta path. et microbiol. Scandinav.* **23**: 242–251, 1946.
3. Teilum, G. Arrhenoblastoma—Androblastoma. Homologous ovarian and testicular tumors II., *Acta path. et microbiol. Scandinav.* **23**: 252–264, 1946.
4. Schiller, W.: Mesonephroma ovarii, *Am. J. Cancer* **35**: 1–21, 1939.
5. Lecène, P.: *see* Moulonget, P. (14).
6. Varangot, J.: Les tumeurs de la granulosa, *J. de chir.* **51**: 651–681 (May) 1938.
7. Plate, W. P.: Eine seltene Form eines Granulosazelltumors des Ovariums, das sog. "Folliculome lipidique" (Lecène). *Arch. f. Gynäk.* **153**: 318–332, 1933.
8. Traut, H. F., and Butterworth, J. S.: The theca, granulosa, lutein cell tumors of the human ovary and similar tumors of the mouse's ovary, *Am. J. Obst. & Gynec.* **34**: 987–1006 (Dec.) 1937.

9. HENDERSON, D. N.: Granulosa and theca cell tumors of the ovary, *Am. J. Obst. & Gynec.* **43**: 194–210 (Feb.) 1942.
10. DOUGAL, D. A.: Granulosa cell tumor of tubular or adenomatous type, *J. Obst. & Gynec. Brit. Emp.* **52**: 370–371 (Aug.) 1945.
11. VARANGOT, J.: Les tumeurs de la granulosa (folliculomes de l'ovaire). Paris, Louis Arnette, 1937.
12. CHRISTIAN, E.: Un cas d'épithélioma à granulations de lutéine, d'origine probablement ovarienne, *Soc. anatomique* ann. 85, s. 6, **12**: 639–641, 1910.
13. GREVLE, A.: Granulosasvulster, Norsk mag. f. laegevidensk. **97**: 918–926 (Sept.) 1936.
14. MOULONGUET, P.: Les diagnostics anatomo-cliniques de Paul Lecène, recueillis par ses élèves. Appareil génital de la femme, Masson, Paris, 1932, vol. 1, part 2.
15. HUGGINS, C., and MOULDER, P. V.: Estrogen production by Sertoli cell tumors of the testis, *Cancer Research* **5**: 510–514 (Sept.) 1945.
16. NOVAK, E.: Gynecological and Obstetrical Pathology: With Clinical and Endocrine Relations, ed. 2, Philadelphia and London, W. B. Saunders Company, 1947.
17. SAND, K.: The evolution in the study on the sex hormones, *Zacchia* **3**: 181–199, 1939.
18. KLINEFELTER, H. F., JR.; REIFENSTEIN, E. C., JR., and ALBRIGHT, F.: Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism, and increased excretion of follicle-stimulating hormone, *J. Clin. Endocrinol.* **2**: 615–627 (Nov.) 1942.
19. DEL CASTILLO, E. B.; TRABUCCO, A., and DE LA BALZE, F. A.: Syndrome produced by absence of the germinal epithelium without impairment of the Sertoli or Leydig cells, *J. Clin. Endocrinol.* **7**: 493–502 (July) 1947.
20. MASSON, P.: Deux cancers Leydigiens de l'homme, *Rev. canad. de biol.* **2**: 168–243 (May) 1943.
21. PEDERSEN, J.: Virilizing ovarian tumors, *J. Clin. Endocrinol.* **7**: 115–129 (Feb.) 1947.
22. PICK, L.: Ueber Neubildungen am Genitale bei Zwittern nebst Beiträgen zur Lehre von den Adenomen des Hodens und Eierstockes, *Arch. f. Gynäk.* **76**: 191–281, 1905, (case p. 251).
23. SCHICKELE, G.: Adenoma tubulare ovarii (testiculare), *Beitr. z. Geburtsh. u. Gynäk.* **11**: 263–268, 1907.
24. GOLDBERG, M. B., and MAXWELL, A. F.: Bilateral arrhenoblastoma without masculinization: adenoma testiculare of Pick. Proc. of 29th annual meeting of Assoc. for Study of Internal Secretions, *J. Clin. Endocrinol.* **7**: 456 (June) 1947.
25. GREENBLATT, R. B.; GREENHILL, J. P., and BROWN, W. R.: Variations of lipid content in certain ovarian tumors, *Am. J. Obst. & Gynec.* **37**: 929–939 (June) 1939.
26. ØSTERGAARD, E.: Feminizing tumor of the testis: presumably aberrant adrenocortical tumor, *J. Clin. Endocrinol.* **7**: 438–445 (June) 1947.
27. MEYER, R.: Tubuläre (testiculäre) und solide Formen des Andreioblastoma ovarii und ihre Beziehung zur Vermännlichung, *Beitr. z. path. Anat. u.z. allg. Path.* **84**: 485–520 (March) 1930.

CORTICAL STEROID EXCRETION IN EDEMA OF PREGNANCY, PRE-ECLAMPSIA, AND ESSENTIAL HYPERTENSION*

LOUIS TOBIAN, JR., M.D.

From the Department of Internal Medicine and the Department of Obstetrics and Gynecology, Southwestern Medical College, Dallas, Texas

THE syndrome seen in desoxycorticosterone intoxication is in many respects strikingly similar to toxemia of late pregnancy (pre-eclampsia and eclampsia). In both syndromes one may find hypertension (1, 2, 3, 4), edema (2, 3, 4, 5), and albuminuria (2, 4, 6).

In both syndromes the hypertension is greatly alleviated by drastic dietary sodium restriction (7, 8, 9). In both syndromes the hypertension and albuminuria may be markedly increased by an excessive sodium intake in the diet (6, 7).

Excessive DCA administration to animals usually causes atrophy of the adrenal cortex, presumably because of an inhibition of corticotropic hormone secretion by the anterior pituitary (10, 11, 12). Paralleling the DCA findings, Fauvet found abnormally small adrenals in women dying of eclampsia (13) and reported a decreased concentration of corticotropic hormone in the serum of eclamptic women (14).

Women with essential hypertension have a greatly increased susceptibility to toxemia of pregnancy (15a). They are also more susceptible to the pressor effects of DCA (16).

Renal disease which produces hypertension also increases susceptibility to toxemia. Unilateral nephrectomy (17) and Masugi nephritis (18) in animals increase the toxic effects of DCA.

The foregoing considerations suggested the possibility that toxemia of pregnancy may be related to an increased concentration of desoxycorticosterone-like steroids in the body fluids or cells. Therefore, urinary corticosteroid excretion was measured in normal and toxemic pregnant women. Determinations were also made on normal individuals and on patients with essential hypertension.

Criteria for clinical classification

The following criteria were satisfied before the diagnosis of pre-eclampsia was made:

1) The occurrence in late pregnancy of a definite increase in diastolic blood pressure or proteinuria over the pre-pregnant level.

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2) A decrease of hypertension or albuminuria after delivery, if these signs had persisted despite therapy up to delivery.

Women were considered as having "minimal or no edema" when they either had no clinical edema at all or had only minimal pitting edema of their feet and ankles. Women were considered as having "excessive edema," when their face, hands, and feet were swollen considerably and when they showed large postpartum losses in weight.

METHODS

All studies on pregnant women were made between the thirty-first and fortieth weeks of pregnancy.

Twelve-hour overnight urine samples were collected in bottles containing 5 cc. of toluene and extracted within eight hours of the end of the collection. Aliquots of 150 cc. of the urine were acidified with 12 N H_2SO_4 to pH 1 as determined with a glass electrode. The aliquots were then immediately extracted once with 300 cc. of redistilled ethyl acetate and once with 150 cc. of the ethyl acetate. The ethyl acetate extracts were combined and extracted twice with 90 cc. portions of 0.1 N H_2SO_4, then twice with 150 cc. quantities of 2 N NaOH and then 5 times with 75 cc. portions of distilled water.

The purified ethyl acetate extracts were then evaporated to dryness *in vacuo*, the surrounding water bath never exceeding a temperature of 42° C.

The residue was brought into solution with 3 cc. of absolute ethyl alcohol, and corticosteroids were determined, utilizing in the main the procedure of Loewenstein (19). This involves cleavage of the 20, 21-ketol side chain of the corticosteroid by oxidation with periodic acid, with the release of formaldehyde (20). Formaldehyde is then determined by the colorimetric method of MacFadyen (21).

To the residue dissolved in 3 cc. of absolute ethanol, 20 cc. of water was added, and quickly thereafter 4 cc. of the periodate solution (0.01 M KIO_4 dissolved in .036M H_2SO_4 solution). The oxidation mixture was immediately shaken and allowed to react for 20 minutes at room temperature with occasional shaking.

Then 0.5 cc. of freshly prepared 6 per cent $SnCl_2$ solution dissolved in 1:1 concentrated HCl was added to terminate oxidation. A white precipitate appeared on addition of the Sn Cl_2 solution.

The mixture was then filtered through Whatman #12 paper to prevent turbidity in some specimens and a 15 cc. aliquot of the filtrate was placed in a standard 25×200 mm. "NPN" tube. The tube was immersed in a bath of ice water and 20 cc. of concentrated H_2SO_4 was slowly added to the tube. Then 1 cc. of a 7 per cent chromotropic acid solution was added and the contents mixed with a footed stirring rod.

The tubes were then placed in a boiling water bath for 30 minutes, were brought to room temperature and the solutions were read in an Evelyn colorimeter, using an Evelyn #565 filter.

An aliquot of 150 cc. of distilled water was always carried through the entire analytic procedure and this solution served as a blank.

It is realized that this procedure is not necessarily specific for "corticosteroids," such as the crystalline, physiologically active steroids that have been isolated from adrenal glands. Any compound with a free, terminal, vicinal glycol or hydroxyketone group will also release formaldehyde on HIO_4 oxidation. Furthermore, it is possible that there are compounds present other than formaldehyde which produce a lavender color when treated with chromotropic acid. They are said by MacFadyen to be few (21).

Because of this possible nonspecificity, it was thought that any simple procedures which would remove contaminating substances from the final residue without greatly diminishing the neutral corticosteroids would be desirable additions. For this reason the acid and alkali washes of the ethyl acetate extracts were included in the procedure.

Ethyl acetate was chosen for a solvent because it will more readily extract polar, highly hydroxylated corticosteroids such as 17-hydroxycorticosterone or steroids with solubility properties like the sodium-retaining steroid recently isolated by Thatcher and Hartman (22). Moreover, its low density compared to water facilitates washing (in contrast to chloroform).

By extracting with relatively large volumes of ethyl acetate, emulsions were avoided, even in urines containing considerable protein.

The color interference mentioned by Daughaday *et al.* (23) was not encountered, and it is possible that the interfering substances were removed in the alkali washes, which were seen to extract a brown pigment from the ethyl acetate fraction.

The formaldehyde distillation procedure described by Daughaday *et al.* (23) appears

TABLE 1. EXCRETION OF FORMALDEHYDOGENIC CORTICOSTEROIDS (MG./12 HRS.) BY PREGNANT AND NON-PREGNANT FEMALES

Normal women	Normal pregnant women with minimal or no edema	Pre-eclamptic women with minimal or no edema	Pregnant women with excessive edema but without hypertension or albuminuria	Pre-eclamptic women with excessive edema
.27	.54	.77	1.31	.95
.33	.60	.85	1.47	1.04
.35	.73	.86		1.07
.45	.75	.87		1.23
.47	.77	.96		1.26
.53	.87			1.32
.54	.88			1.39 (twins)
.55	.91			1.46
.56	.94			1.48
.66	1.0			1.57
	1.01			1.76
	1.05			2.06 (twins)
	1.07			
	1.08			
	1.13			
	1.15			
	1.18			
	1.40 (twins)			
Mean				
.47	.95	.86	1.39	1.38

to be a sound addition to this method and it is planned to adopt this feature in future determinations. However, even without the distillation it appears that our procedure analyzes essentially the same compounds as Daughaday and co-workers (23), since our normal values are almost identical with theirs.

With periodic acid treatment, each mole of corticosterone or desoxycorticosterone yields 1 mole of formaldehyde. We have arbitrarily chosen to express our results as milligrams of desoxycorticosterone excreted per 12 hours. This figure is arrived at by multiplying the milligrams of formaldehyde found, by a factor 11.0, since a mole of desoxycorticosterone weighs 11.0 times as much as a mole of formaldehyde.

EXCRETION OF FORMALDEHYDOGENIC CORTICOSTEROIDS BY SEVERAL CLINICAL GROUPS

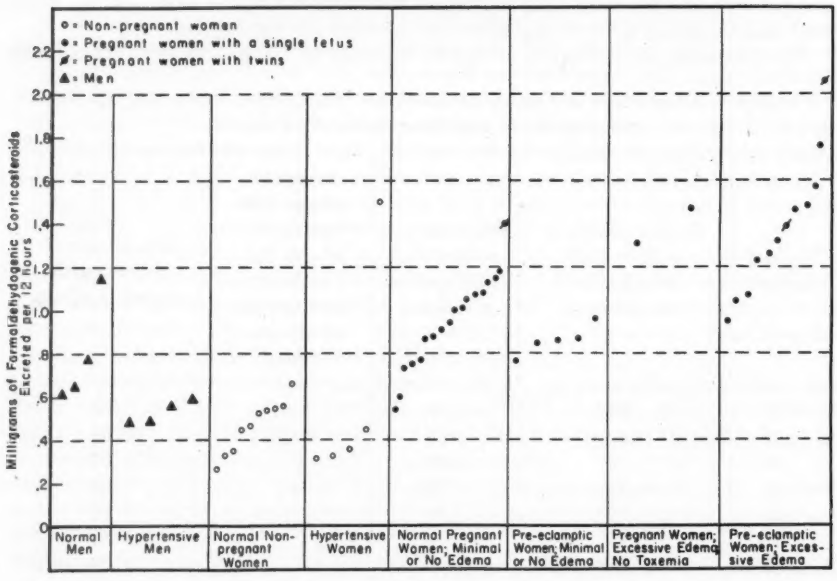

FIG. 1

Following the suggestion of Daughaday *et al.* (24), the cortical steroids will be called "formaldehydogenic corticosteroids" throughout the rest of the paper. To save space this will usually be abbreviated to "HCHO" corticosteroids.

RESULTS

According to the data presented in Table 1 and Figure 1, normal pregnant women in the last trimester excreted about twice as much "HCHO" corticosteroid per 12 hours as normal non-pregnant women.

The results also show that 2 of the 3 women with twins excreted con-

TABLE 2. FORMALDEHYDOGENIC CORTICOSTEROID EXCRETION (MG./12 HRS.) OF PREGNANT WOMEN WITH EQUIVALENT AMOUNTS OF EXCESSIVE EDEMA AND VARYING DEGREES OF PRE-ECLAMPSIA (WOMEN WITH TWINS NOT INCLUDED)

	Mild pre-eclamptics	Moderate pre-eclamptics	Severe pre-eclamptics
	1.07	1.04	.95
	1.26	1.23	1.76
	1.32		
	1.46		
	1.48		
	1.57		
Mean	1.36	1.14	1.36

siderably more "corticosteroid" than any single-fetus woman in her clinical group.

The mean corticosteroid excretion of women with toxemia and excessive edema was about 45 per cent greater than that of the normal pregnant women with minimal or no edema.

However, the corticosteroid excretion of toxemic women without excessive edema was no greater than that of normal pregnant women without edema.

Two cases of so-called "excessive edema of pregnancy" without hypertension or albuminuria showed an increased excretion value similar to that seen in women with excessive edema and toxemia.

In cases with equivalent amounts of edema we found no correlation between the blood pressure level and the "HCHO" corticosteroid excretion

TABLE 3

Group No.	Type of subject	No. in group	Average formaldehydogenic corticosteroid excretion (mg./12 hrs.)	Standard deviation of groups
I	Normal non-pregnant women	10	0.471	.199
II	Pregnant women with minimal or no edema	22	0.908	.262
III	Pregnant women with excessive edema	12	1.327	.464

TABLE 4

Difference between means	Standard error of difference between means	T value	Odds against the observed differences between means being due to chance
Group II-Group I .908 − .471 = .437	.084	5.2	2,000,000 to 1
Group III-Group II 1.327 − .908 = .419	.145	2.89	250 to 1

value. In Table 2, all the toxemic women with a single fetus and a roughly equivalent amount of excessive edema are divided into three clinical groups in ascending order of clinical severity as judged by the degree of hypertension. The values in the table show that increasing levels of blood pressure in toxemia are not associated with increased "HCHO" corticosteroid excretion.

On the whole the data indicate that late pregnancy itself is associated with an increased "HCHO" corticosteroid excretion, which is even further increased in women having excessive edema in late pregnancy.

Table 3 shows the mean "HCHO" corticosteroid excretion, with its standard deviation, for each of these three groups: 1) normal non-pregnant women, 2) all pregnant women with minimal or no edema, and 3) all preg-

TABLE 5. EXCRETION OF FORMALDEHYDOGENIC CORTICOSTEROIDS (MG./12 HRS.) BY NORMAL AND HYPERTENSIVE SUBJECTS

Normal women	Hypertensive women	Normal men	Hypertensive men
.27	.32	.62	.49
.33	.33	.65	.49
.35	.36	.78	.56
.45	.45	1.15	.59
.47	1.50		
.53			
.54			
.55			
.56			
.66			
Mean .47	.59	.80	.53

nant women with excessive edema. Since twin pregnancy probably increases the "HCHO" corticosteroid excretion and constitutes a separate variable, all women with twins were excluded from these groups. The mean "HCHO" corticosteroid excretion of Group III was 46 per cent greater than that of Group II.

Table 4 shows the difference between the means of Groups I and II and of Groups II and III, along with the standard error of these differences, and the odds against the observed differences being due to chance. We believe that the observed differences between these means are significant.

Figure 1 and Table 5 show the "HCHO" corticosteroid excretion value in hypertensive men and women as well as in normal men and women. Except for one hypertensive female, the patients with essential hypertension had no greater "HCHO" corticosteroid excretion than normal subjects.

DISCUSSION

Relationship between edema of pregnancy and the extra "HCHO" corticosteroid excretion associated with edema of pregnancy

Dexter and Weiss made a very careful and excellent clinical study of the edema associated with pregnancy. They concluded that "the etiology of the generalized edema of pregnancy cannot be explained by the well recognized mechanical causes of edema formation such as increased hydrostatic pressure in the capillaries, increased capillary permeability to protein, or hypoproteinemia. The edema is not due primarily to cardiac failure, anemia, vitamin B_1 deficiency, myxedema, or excessive ingestion of sodium salts, although many of these factors may at times play an important secondary role. By exclusion, a primary humoral etiology is suspected" (15b).

Earlier in this paper it was pointed out that DCA and other adrenal products can cause sodium retention and edema (1, 2, 3, 4, 5, 8, 16). We have also shown in the preceding section that pregnant women with edema have an increased excretion of "HCHO" corticosteroids. These interrelated facts strongly suggest that the extra corticosteroids or their precursors are the actual cause of the sodium retention and edema.

This concept cannot be considered as proved until all the actual hormones secreted during pregnancy and their metabolites have been identified and assayed. There may be other substances with edema-forming properties that are present in extra large amounts in edema of pregnancy. Certainly increased excretion rates of estrogens and pregnanediol are not associated with edema of pregnancy.

Relationship between "HCHO" corticosteroid excretion and the adrenal cortex

The "HCHO" corticosteroids measured were *excreted* and may very well not have been *secreted* in the body as such. They may be only the metabolites of steroid hormones which are actually secreted.

However, others have shown that in the non-pregnant individual the "HCHO" corticosteroid excretion level is a valid index of the secretion rate of adrenal cortical hormones, such level being elevated in Cushing's syndrome and other hyperadrenal states and being decreased in Addison's disease (24). In support of this we found a very high excretion of "HCHO" corticosteroids (1.7 mg./12 hrs.) in a man with a severe burn, a condition which is usually accompanied by adrenal cortex hypersecretion (25).

The maternal adrenal cortex is hypertrophied and richly laden with lipoids in late pregnancy. Venning has reported sizable increases in the secretion of "glycogenic corticoids" (26) and phosphomolybdate-reducing lipoids (27) in that stage of pregnancy. These findings indicate that the maternal adrenal cortex is very likely in a state of hypersecretion in late pregnancy and is probably the source of a large fraction of the increased "HCHO" corticosteroids we found to be excreted at that time.

There is no direct evidence that any endocrine gland other than the maternal adrenal cortex contributes to the "HCHO" corticosteroids formed in the urine. However, it has been reported that women with Addison's disease experience a marked relief of symptoms in the last months of pregnancy (28, 29). Their need for substitution therapy diminishes or disappears altogether, only to return at the termination of pregnancy (30). These findings suggest that in late pregnancy, sources other than the maternal adrenal cortex normally show an increased secretion of substances whose effect is similar to that of the adrenal cortex hormone. It is quite possible that these corticomimetic hormones may partially contribute to the increased "HCHO" corticosteroids excreted in late pregnancy. Studies of the "HCHO" corticosteroid excretion in pregnant women with Addison's disease would furnish valuable information concerning this possibility.

Relationship of "HCHO" corticosteroid excretion and pre-eclamptic hypertension

The "HCHO" corticosteroid excretion could not be correlated with increases in blood pressure seen in pre-eclampsia. However, the findings do not exclude the possibility that a steroid not mesaured by this method may be fundamentally important in the causation of the hypertension and albuminuria of pre-eclampsia and eclampsia.

It is not known what effect the decreased glomerular filtration often

seen in pre-eclampsia has on the renal clearance of the "HCHO" corticosteroids.

Relationship of "HCHO" corticosteroid excretion and essential hypertension

"HCHO" corticosteroid excretion was also not abnormal in most patients with essential hypertension. This is fairly good evidence against marked adrenal cortex hypersecretion in most patients with essential hypertension. However, it does not exclude the possibilities that 1) small increases in adrenal cortex secretion or 2) normal rates of secretion with alteration in the metabolism of the hormone after is is secreted, may be importantly involved in the pathogenesis of essential hypertension.

SUMMARY

1. Corticosteroid excretion in urine was estimated by a modified Loewenstein method.

2. Pregnant women in the last trimester excreted twice as much corticosteroid as non-pregnant women.

3. Pregnant women with excessive edema excreted about 46 per cent more corticosteroid than pregnant women with minimal or no edema. This difference is statistically significant.

4. The extra corticosteroids associated with edema of pregnancy or their precursors may perhaps be the cause of the renal retention of sodium and water producing the edema.

5. Women with twins showed a greater corticosteroid excretion than women with a single fetus.

6. The level of corticosteroid excretion could not be correlated with the elevation of blood pressure seen in pre-eclampsia.

7. Most patients with essential hypertension showed a normal corticosteroid excretion.

Acknowledgment

The author greatly appreciates the help he received from the following individuals: Max Huffman, T. R. Harrison, M. F. Mason, Joe Touchstone, W. F. Mengert, A. W. Diddle, Ray Jennet, Ray Rimmer, Mary Harriet Lott, E. S. Bromberg, and H. A. Stiff.

REFERENCES

1. Perera, G. A.; Knowlton, A. I.; Lowell, A., and Loeb, R. F.: Effect of desoxycorticosterone acetate on the blood pressure of man, *J.A.M.A.* **125**: 1030–1035 (Aug.) 1944.
2. Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone esters: certain effects in the treatment of Addison's disease, *J.A.M.A.* **113**: 1725–1731 (Nov.) 1939.

3. THORN, G. W.; DORRANCE, S. S., and DAY, E.: Addison's disease: evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients, *Ann. Int. Med.* **16**: 1053–1096 (June) 1942.
4. ALTSCHULE, M. D., and ZAMCHECK, N.: Studies of the circulation and respiration in a patient with anasarca following administration of cortin and sodium chloride, *J. Clin. Endocrinol.* **2**: 269–271 (April) 1942.
5. CLINTON, M., and THORN, G. W.: Effect of desoxycorticosterone acetate administration on plasma volume and electrolyte balance of normal human subjects, *Bull. Johns Hopkins Hosp.* **72**: 255–263 (May) 1943.
6. SELYE, H.; HALL, C. E., and ROWLEY, E. M.: Malignant hypertension produced by treatment with desoxycorticosterone acetate and sodium chloride, *Canad. M.A.J.* **49**: 88–92 (Aug.) 1943.
7. STRAUSS, M. B.: The toxemias of pregnancy, *New York State J. Med.* **40**: 810–818 (May) 1940.
8. PERERA, G. A., and BLOOD, D. W.: The relationship of sodium chloride to hypertension, *J. Clin. Investigation* **26**: 1109–1118 (Nov.) 1947.
9. KNOWLTON, A. I.; LOEB, E. N.; STOERK, H. C., and SEEGAL, B. C.: Desoxycorticosterone acetate; the potentiation of its activity by sodium chloride. *J. Exp. Med.* **85**: 187–197 (Feb.) 1947.
10. SELYE, H., and DOSNE, C.: Changes produced by desoxycorticosterone overdosage in the rat, *Proc. Soc. Exper. Biol. & Med.* **44**: 165–167 (May) 1940.
11. SARASON, E. L.: Morphologic changes in the rat's adrenal cortex under various experimental conditions, *Arch. Path.* **35**: 373–390 (March) 1943.
12. GREEP, R. O., and DEANE, H. W.: Cytochemical evidence for the cessation of hormone production in the zona glomerulosa of the rat's adrenal cortex after prolonged treatment with desoxycorticosterone acetate, *Endocrinology* **40**: 417–425 (June) 1947.
13. FAUVET, E.: Eklampsie and Nebennieren, *Klin. Wchnschr.* **16**: 1356–1358 (Sept.) 1936.
14. FAUVET, E., and MÜNZNER, L.: Das corticotrope Hormon der Hypophyse bei normalen und pathologischen Schwangerschaften, *Klin. Wchnschr.* **16**: 675–677 (May) 1937.
15. DEXTER, L., and WEISS, S.: Preclamptic and Eclamptic Toxemia of Pregnancy. Boston, Little, Brown & Co. 1941, (a) p. 187, (b) p. 57.
16. PERERA, G. A., and BLOOD, D. W.: Pressor activity of desoxycorticosterone acetate in normotensive and hypertensive subjects, *Ann. Int. Med.* **27**: 401–404 (Sept.) 1947.
17. SELYE, H., and PENTZ, E. I.: Pathogenetical correlations between periarteritis nodosa, renal hypertension and rheumatic lesions, *Canad. M.A.J.* **49**: 264–272, (Oct.) 1943.
18. KNOWLTON, A. I.; STOERK, H.; SEEGAL, B. C., and LOEB, E. N.: Influence of adrenal cortical steroids upon the blood pressure and the rate of progression of experimental nephritis in rats, *Endocrinology* **38**: 315–324 (May) 1946.
19. LOEWENSTEIN, B. E.; CORCORAN, A. E., and PAGE, I. H.: Determination of corticosteroids in urine, *J. Clin. Endocrinol.* **6**: 481 (June) 1946.
20. FIESER, L. F.; FIELDS, M., and LIEBERMAN, S.: Concerning the characterization of possible cortical hormone metabolites in urine, *J. Biol. Chem.* **156**: 191–201 (Nov.) 1944.

21. MacFadyen, D. A.: Estimation of formaldehyde in biological mixtures, *J. Biol. Chem.* **158:** 107–133 (March) 1945.
22. Thatcher, J. S., and Hartman, F. A.: Sodium retaining substances of the adrenal, *Arch. Biochem.* **10:** 195–203 (June) 1946.
23. Daughaday, W. H.; Jaffe, H., and Williams, R. H.: Chemical assay for "cortin" determination of formaldehyde liberated on oxidation with periodic acid, *J. Clin. Endocrinol.* **8:** 166–174 (Feb.) 1948.
24. Daughaday, W. H.; Jaffe, H., and Williams, R. H.: Adrenal cortical hormone excretion in endocrine and nonendocrine disease as measured by chemical assay, *J. Clin. Endocrinol.* **8:** 244–256 (March) 1948.
25. Browne, J. S. L., and Venning, E. H.: The response of the adrenal cortex to disease and trauma, *Tr. A. Am. Physicians* **60:** 16–17, 1947.
26. Venning, E. H.: Adrenal function in pregnancy, *Endocrinology* **39:** 203–220 (Sept. 1946.
27. Heard, R. D. H.; Sobel, H., and Venning, E. H.: The neutral lipide-soluble reducing substances of urine as an index of adrenal cortical function, *J. Biol. Chem.* **165:** 699–710 (Oct.) 1946.
28. Crabtree, E. G.: Urological Diseases of Pregnancy. Boston, Little, Brown & Co., 1942, p. 369.
29. Goldzieher, M. A.: The Adrenal Glands in Health and Disease. Philadelphia, F. A. Davis Co., 1945, p. 548.
30. Soffer, L. J.: Diseases of the Adrenals. Philadelphia, Lea & Febiger, 1946, p. 154.

THERAPEUTIC STUDIES IN HYPERTHYROIDISM: PROPYLTHIOURACIL

PAUL STARR, M.D.*, DONALD W. PETIT, M.D.,†
LESTER MEISTER, M.D.§ AND ROBERT
L. STIRRETT, M.D.†

From the School of Medicine, University of Southern California, and the Endocrine Clinic, Los Angeles County Hospital, Los Angeles, California

INTRODUCTION

THE new methods of treating hyperthyroidism with the antithyroid drugs and radioactive iodine represent no fundamental change from the ancient methods of attack upon the disease. They are, respectively, merely forms of chemical and radiation thyroidectomy and, therefore, are no more functional than the method employed by our grandfathers of destroying the thyroid by the injection of boiling water.

The ideal treatment for hyperthyroidism would be based on a knowledge of the disorder causing the disease and a procedure to correct that disorder, returning the thyroid to its normal position in metabolic physiology rather than removing it from the endocrine chain. The possibility of such a solution is clinically demonstrable (1). For example, in the case of Mrs. L., shown in Figure 1, a puerperal hyperthyroidism of severe and unmistakable degree disappeared during the endocrine reaction induced by weaning her baby. A similar restoration of normal relations is shown in Figure 2, in which Miss Grace DeF. with moderately severe hyperthyroidism returned to normal after a few injections of chorionic gonadotropin.

PATHOLOGY

The antithyroid drugs derived from thiouracil do not seem to promote a restoration to normal but rather exaggerate the pathology of the disease, while paradoxically frustrating the formation of an increased amount of thyroid hormone. The intense hyperplasia resulting from the prolonged use of propylthiouracil is well illustrated in Figure 3, which shows a specimen taken from the gland of a patient who had received the drug for eight months (Miss L. S.). The small accumulation of colloid is due to the preoperative use of iodine: otherwise, as has been well shown by others, no colloid would be seen. The pathology resulting in this case may well be

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* Professor and Chairman, Department of Medicine.

† Assistant Professor, School of Medicine.

§ Assistant Clinical Professor of Medicine, College of Medical Evangelists, Los Angeles. Instructor in Medicine, University of Southern California.

Technical assistance of Jacqueline Gerjuoy.

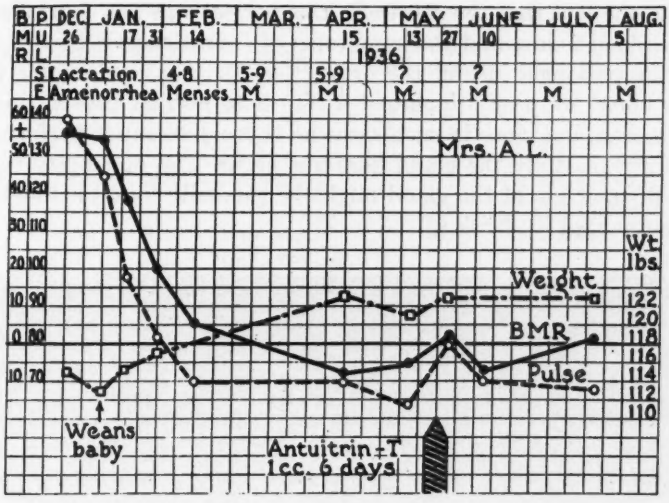

FIG. 1. (Case 1). Mrs. A. L. Example of remission of hyperthyroidism coincident with cessation of lactation and return of menstruation. (Reprinted from Starr, P., and Pomerenze, H.: *Ann. Int. Med.* **15**: 226–244 (Aug.) 1941. (1).

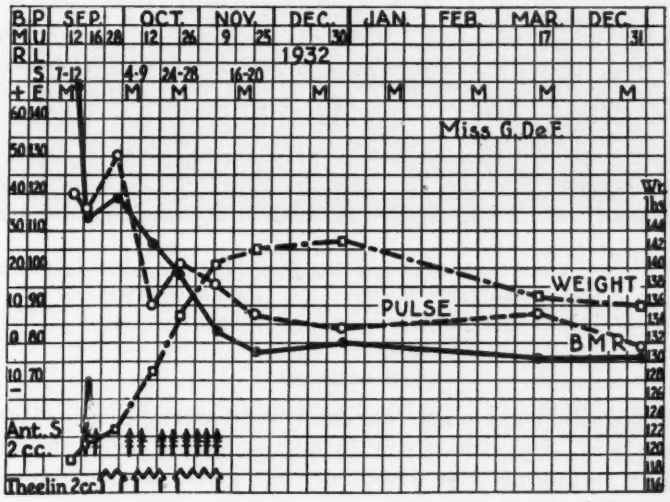

FIG. 2. (Case 2). Miss G. DeF. Example of remission of hyperthyroidism coincident with treatment with chorionic gonadotropin and theelin. (Reprinted from Starr, P., and Pomerenze, H.: *Ann. Int. Med.* **15**: 226–244 (Aug.) 1941. (1).

related to the fact that the disease in this patient was not controlled. The elevated blood iodine and the symptoms of thyrotoxicosis persisted even during the prolonged use of the drug (Fig. 9). It is conceivable that in patients cured by propylthiouracil a return to normal thyroid histology would be seen, but since in such cases no thyroidectomy is performed the opportunity to study the gland does not occur. The possibility that this involuted condition of the gland might be generally found is indicated in one case reported by Frisk (2).

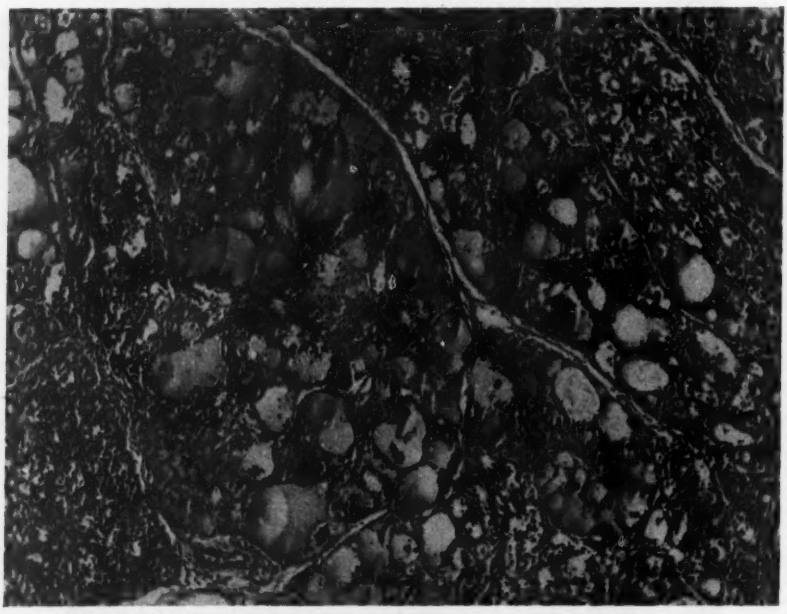

FIG. 3. Thyroid tissue removed at operation from Miss L. S. after eight months' administration of large doses of propylthiouracil. Iodine was administered for several weeks preoperatively. Intense hyperplasia and desquamation are shown (case 11, Fig. 9).

PROCEDURE

Serum protein-bound iodine[1] was determined several times before beginning treatment. Propylthiouracil[2] in dosage ranging from 50 mg. three times daily to 150 mg. four times daily was given to a series of patients

[1] In the present study, protein-bound blood iodine was determined throughout by Doctor A. L. Chaney, Glendale, California.

[2] Propylthiouracil ("Probacil") was generously provided by Doctor Stanton M. Hardy, Medical Director, Lederle Laboratories.

TABLE 1

Patient	Propylthiouracil: Duration of treatment (months)	Propylthiouracil: Daily dose (mg.)	Present clinical condition	Toxic reaction	Remarks
I.B.	11	200	Controlled	?	No relapse when treatment discontinued after 11 mo.
D.C.	4½	300	Controlled	0	Treatment continued.
M.C.	2	200	Uncontrolled	0	Changed to methylthiouracil after 2 mo.
B.C.	10	300	Uncontrolled	0	Treatment discontinued.
K.D.	7	150	Controlled, with PBI* below 5, for 4 mo.	0	Treatment continued.
M.D.	9	300	Controlled	0	Relapse when treatment discontinued after 9 mo.
E.D.	6	300	Controlled		Treatment continued.
E.F.	9	300	Controlled, with PBI below 5, for 2 mo.	0	Relapse when treatment discontinued after 9 mo.
G.G.	2	600	Controlled	0	Treatment continued.
L.G.	11	200	Controlled incompletely	0	Not cured.
J.H.	15	150	Uncontrolled	0	Unchanged.
O.H.	2	600	Uncontrolled		Thyroidectomy.
V.L.	9 1	600 150	Controlled Uncontrolled	Leukopenia	Thyroidectomy.
H.L.	8	200	Controlled	0	Treatment continued.
U.M.	2	300	Uncontrolled	0	Thyroidectomy.
W.N.	4	150	Uncontrolled	?	Thyroidectomy.
B.P.	14	300	Controlled	0	Relapse when treatment discontinued after 14 mo.
E.P.	1	600	?	Leukopenia	?
P.R.	5 2	400 600	Partial control Controlled		Thyroidectomy.
C.R.	10	300	Controlled	0	Treatment continued.
L.S.	8	300	Controlled	0	Thyroidectomy.
M.S.	9	200	Controlled	Leukopenia	Relapse when treatment discontinued after 9 mo.
M.D.S.	9	300	Controlled	0	Treatment continued.
L.T.	12	300	Controlled	0	Treatment continued.
D.T.	8	150	Controlled	0	Relapse when treatment discontinued after 8 mo.
R.W.	4	300	Controlled	0	Treatment continued.
T.W.	4	600	Controlled	Leukopenia	Died.
K.Y.	9	200	Controlled	Leukopenia	Relapse after treatment had been discontinued for 9 mo. Controlled when treatment started again.

* Protein-bound blood iodine.

having all varieties of hyperthyroidism. During the first month, protein-bound blood iodine determinations were made at short intervals for the purpose of determining the rate of fall in proportion to the dosage given. The results of this study are shown in the following section. The drug was then continued indefinitely, patients reporting once a week for clinical estimation and differential white blood count. The progress of the treatment was followed chiefly with determinations of protein-bound blood iodine, as is shown in Figures 7, 8, and 9. After several months of normal blood iodine values and clinical control of the disease, the drug was discontinued and the reaction of the patient was followed, chemically and clinically.

CLINICAL RESULTS

Forty patients have been treated or have been under treatment since January, 1947. The summary of findings in 28 such cases is shown in Table 1. It is to be seen that in 7 of the 28, or about one-fourth of these patients, the disease was uncontrolled, *i.e.*, the protein-bound blood iodine was not within normal range nor were their clinical symptoms in abeyance. These uncontrolled patients had the following levels of protein-bound blood iodine and of propylthiouracil dosage:

Patient	Duration of therapy (months)	Daily dose (mg.)	Level of protein-bound iodine in serum (micrograms %)
J.H.	15	150	above 9 (Fig. 8)
O.H.	2	600	above 12
W.N.	4	150	above 8
P.R.	3	200	above 9
L.S.	8	300–600	above 10
M.C.	2	200	above 9
B.C.	10	300	above 9

The average duration of treatment of the entire series was six and one half months, ranging from two to fifteen months. The dosage of propylthiouracil ranged from 150 to 600 mg. daily.

Toxicity

Toxicity, as indicated by differential blood counts, developed at some time in 6 of the 40 patients, *i.e.*, 15 per cent of this small series. The white blood cell counts in these cases are shown in Table 2.

In no case was the drug discontinued because of leukopenia.

Relation between dose of propylthiouracil and protein-bound iodine in serum

Figures 4, 5 and 6 show the blood iodine in patients given 150, 300 and

TABLE 2. SIX PATIENTS SHOWING LEUKOPENIC AND GRANULOPENIC REACTION DURING PROPYLTHIOURACIL TREATMENT (FROM A TOTAL OF 40 CASES)

Patient	Duration of therapy before toxic reaction occurred	Daily dose (mg.)	W.B.C. and per cent of polymorphs		Time required for recovery	Dosage at this time (mg.)	Remarks
			before reaction	during reaction			
V.L.	3 weeks	600	5000—50%	2800—14%	—	—	Thyroidectomy
M.D.S.	7 weeks	150	9200—63%	6200—23%	8 weeks (8000—59%)	100	Dose reduced
M.S.	17 days	600	6100—59%	3200—48%	3 days (5400—68%)	150	Dose reduced
V.S.	1 week	150	6750—36%	7400—18%	4 days (7800—41%)	150	No interruption of medication
T.W.	10 days	300	5300—78%	3850—64% 5800—23%	8 weeks (6600—38%)	600	Dose increased to 600 mg. daily
K.Y.	2 months	150	7650—60%	5200—29%	7 weeks (7300—56%)	200	Medication not interrupted

600 mg. per day respectively. It is to be seen from the average iodine curves that there is no striking difference in the immediate reaction to the drug, although in a few instances lower levels are reached in the 600 mg. dose series. Even with 600 mg. per day, the average blood iodine of the group does not reach a normal level.

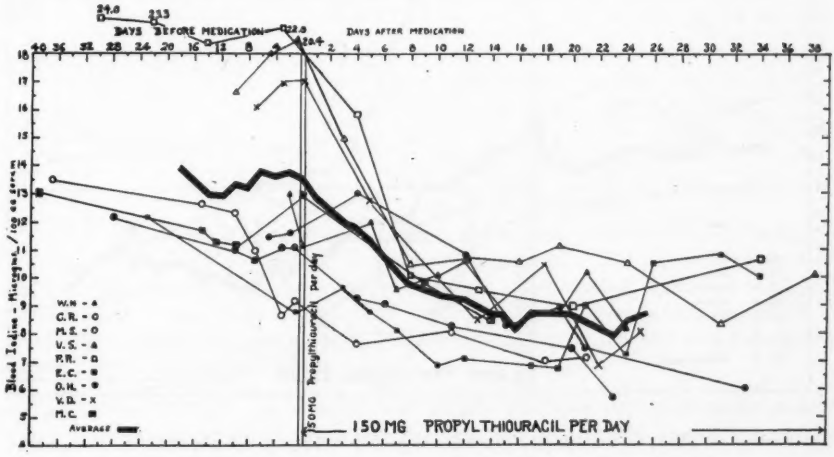

FIG. 4. Serum protein-bound iodine values in 9 patients given 150 mg. propylthiouracil per day.

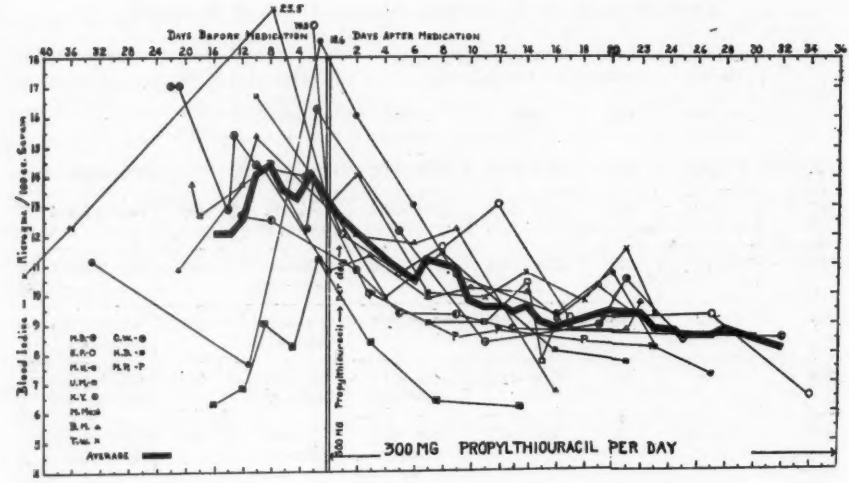
DAYS BEFORE MEDICATION
DAYS AFTER MEDICATION
Blood Iodine — Micrograms / 100 cc. Serum
300 MG PROPYLTHIOURACIL PER DAY
AVERAGE

FIG. 5. Serum protein-bound iodine values in 11 patients given 300 mg. propylthiouracil per day.

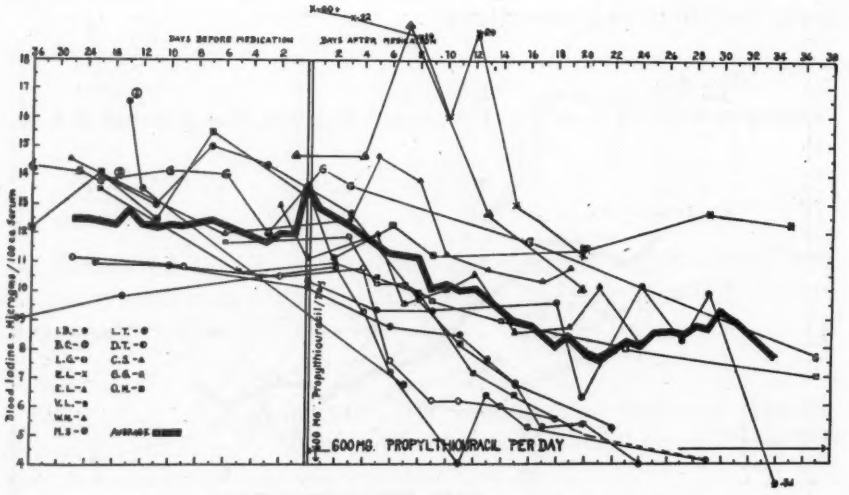
DAYS BEFORE MEDICATION
DAYS AFTER MEDICATION
Blood Iodine - Micrograms / 100 cc. Serum
600 MG. PROPYLTHIOURACIL PER DAY
AVERAGE

FIG. 6. Serum protein-bound iodine values in 13 patients given 600 mg. propylthiouracil per day.

Results of prolonged treatment

The results of prolonged treatment are shown in Figures 7, 8 and 9, in which the individual protein-bound iodine determinations of each patient are shown chronologically. It is to be seen that in a few cases continuous treatment over long periods of time did not control the protein-bound

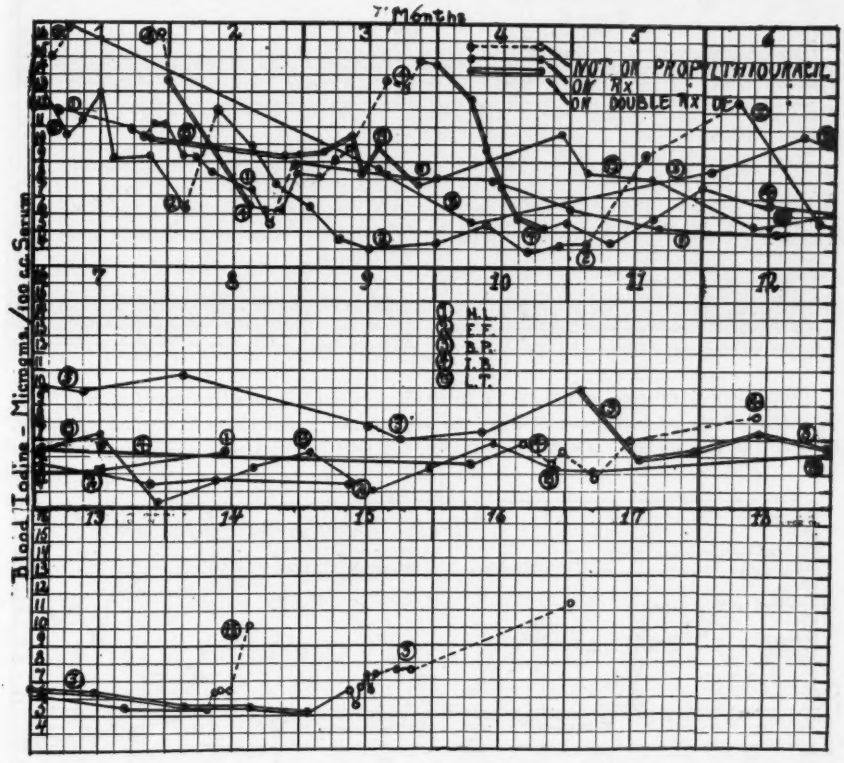

FIG. 7. Serum protein-bound iodine values in 5 patients (dotted lines indicate discontinuance of medication; single lines, usual medication of 300 mg. propylthiouracil daily; double lines, 600 mg. propylthiouracil daily). Cases 1 and 2: treatment continued to date. Case 2: relapse after 4 months of treatment. Case 3: relapse after 14 months of treatment. Case 13: relapse after 13 months of treatment. (In this and subsequent figures, "Rx ē" means "treatment with").

iodine, even though the dosage was large, whereas in other cases a low level was found even though the dosage was relatively small (compare D. T. and L. S. in Fig. 9).

It is evident from a study of the individual curves in Figures 7, 8 and 9 that the daily amount of propylthiouracil required to keep the protein-

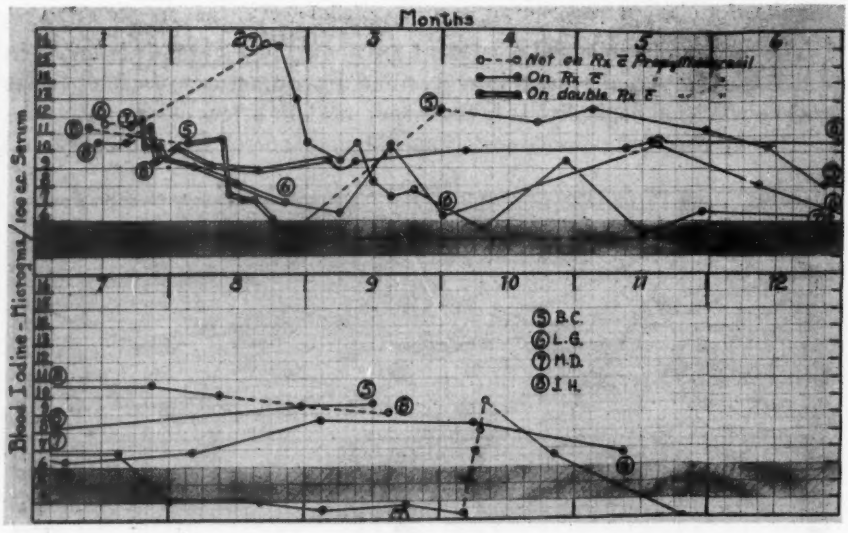

FIG. 8. Serum protein-bound iodine values in 4 patients under treatment with propylthiouracil. Note maintenance of high values in Case 8 and Case 5, normal values in Case 6, and the acute relapse in Case 7 after 9 months of successful treatment.

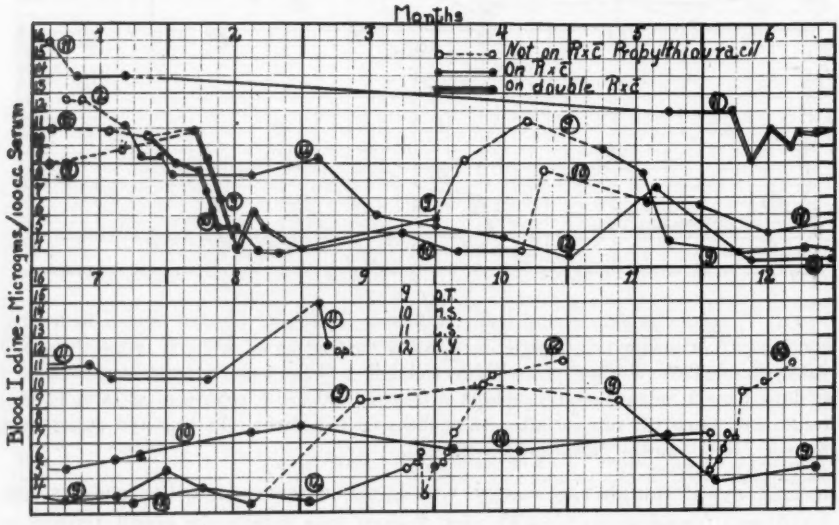

FIG. 9. Serum protein-bound iodine values in 4 patients. Note high values in case 11, in spite of large dosage. Acute relapse occurred in the remaining 3 cases, even when control had been very satisfactory for 9 months, as in Case 12.

bound serum iodine at low levels varies considerably from one patient to the next. For examples, in one patient a small dose such as 100 mg. per day will keep the iodine level low (D.T., No. 9, Fig. 9), whereas in another patient 600 mg. per day will not do so (L. S., No. 11, Fig. 9).

Remissions

Permanent remissions have not been obtained when the medicine was discontinued after several months of satisfactory control. Even though the disease was apparently well suppressed and the protein-bound blood iodine was at a low level, discontinuance of the drug was followed by immediate relapse.

For example, in E.F. (No. 2, Fig. 7) the blood iodine was easily maintained below 5 micrograms per cent for two months, with immediate relapse on omission of medication. She is still taking propylthiouracil and shows a blood iodine level of 4.5 mg. per cent in the ninth month of treatment. Miss D.T. (No. 9, Fig. 9) has had a relapse twice after control of the disease, indicated by blood iodine values below 6 and below 5 micrograms per cent respectively. Miss M. S., Mrs. K. Y., Mrs. I. B., Mrs. B. P., Miss M.D., and Mrs. L.T. have each had relapses after $4\frac{1}{2}$, 5, 6, 6, 6 and 8 months of normal blood iodine findings. Thus, every patient in this series has had a relapse on discontinuance of the medication (Figs. 7, 8 and 9) with the possible exception of I. B. (Fig. 7).

DISCUSSION

Our experience with propylthiouracil would seem to show that the amount of circulating thyroid hormone, as represented roughly by the protein-bound serum iodine, can be reduced in most cases of hyperthyroidism. The use of the drug, therefore, in preparation for a secondary destructive procedure to interrupt the disease (thyroidectomy), is justified. Its use as a prolonged treatment in the hope that the disease will be cured or that an indefinite remission will be induced seems unjustified from this study.

The proportion of cases in which a prolonged remission or cure can be induced by propylthiouracil is extremely important. Different authors report different results. E. B. Astwood (personal communication) finds that 85 per cent of his patients have lasting remissions after discontinuing propylthiouracil. He emphasizes that "a state of hypothyroidism must be maintained for some months in order to obtain this result." Williams (3), reporting on thiouracil, a weaker antithyroid drug than propylthiouracil, states that "of 111 thyrotoxic patients who were treated with thiouracil and had a cessation of therapy, 51 are in remissions that have lasted for 3 to 31 months . . . 33 have remained well for more than eighteen months."

This would indicate that instead of 85 per cent, less than ⅓ have been demonstrated to have a prolonged remission. Frisk (2) states that of 126 patients given prolonged treatment with methylthiouracil, a drug which is as strong as propylthiouracil, 18 patients or approximately 14 per cent were found to have a prolonged remission of at least eighteen months' duration.

If a medication will induce a prolonged, if not permanent, cure of hyperthyroidism in 85 per cent of patients with hyperthyroidism, even though a year's treatment is involved, general use of the drug for this purpose is warranted in spite of the possibility of some drug intoxication. If, on the other hand, only ⅓ or fewer of the patients receive lasting benefit, it would seem that use of the drug in prolonged therapy is unwarranted.

Although the granulopenia in our patients was not severe and was not accompanied by oral or systemic signs of agranulocytosis, we feel that a drug which will cause mild bone marrow depression in so many cases must be used with caution and that it may cause much more dangerous reactions in some cases. Close clinical observation is therefore required while the drug is in use.

SUMMARY

1. Hyperthyroidism was controlled in 21 of 28 patients for from one to ten months during the administration of from 150 to 600 mg. of propylthiouracil daily.

2. The disease was not completely controlled, as indicated by abnormal serum protein-bound iodine levels in 7 of 28 patients.

3. Granulopenia, evidenced by polymorphonuclear percentages ranging from 14 to 48 per cent, was found in 6 patients out of a total of 40 patients to whom the drug was given, indicating a toxic effect on the bone marrow in 15 per cent. Medication was not interrupted in any patient because of this observed granulopenia.

4. The initial fall of protein-bound blood iodine during the first twenty-four days of treatment was not significantly greater during therapy with 600 mg. of propylthiouracil a day than with 150 mg. a day.

5. A relapse, judged by both clinical and chemical findings, occurred in nearly every case in which the drug was discontinued, even when control had been complete chemically for as long as ten months.

CONCLUSION

Propylthiouracil can be used to control hyperthyroidism.

It is frequently ineffective.

It usually will not induce a permanent remission following even prolonged use.

It may produce granulopenia in about 15 per cent of patients.

REFERENCES

1. Starr, Paul, and Pomerenze, Herman: Therapeutic studies in hyperthyroidism, *Ann. Int. Med.* **15**: 226–244 (Aug.) 1941.
2. Frisk, Rune: Treatment of hyperthyroidism with methylthiouracil—results of prolonged treatment, *Acta med. Scandinav.* **129**: 164–183, 1947.
3. Williams, Robert H.; Asper, Samuel P., Jr.; Rogers, Walter F., Jr.; Myers, Jack D., and Lloyd, Charles W.: Persistence of remissions of thyrotoxicosis after cessation of thiouracil therapy, *New England J. Med.* **236**: 737–741 (May 15) 1947.

THE USE OF TRACER DOSES OF RADIOACTIVE IODINE, I^{131}, IN THE STUDY OF NORMAL AND DISORDERED THYROID FUNCTION IN MAN*†

SIDNEY C. WERNER, M.D., EDITH H. QUIMBY, Sc.D., AND CHARLOTTE SCHMIDT, A.B.

From the Departments of Medicine and Radiology, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital in the City of New York

THIS report presents the results of a fact-finding survey concerning the uptake by the thyroid of tracer doses of radioactive iodine of mass 131, eight day half-life, during normal and disordered thyroid gland function in man. This type of study is made possible by the inability of the animal and human organisms to differentiate between the several isotopes of iodine. Thus the radioactive isotopes of iodine are concentrated in, and leave the thyroid gland, in the same manner as the stable form (1, 2). The natural disintegration of the radioactive material produces both gamma and beta rays (3). The beta rays are absorbed within 2 millimeters of tissue. The gamma rays pass through the skin and can be detected readily by a Geiger counter, thus providing a means of determining the presence of the isotope and its actual concentration, and serving as an indicator of the behavior of stable iodine within the body. The highly localized radiation delivered by the beta rays, and the lesser contribution of the gamma rays, have been taken advantage of for therapeutic purposes (4, 5, 6, 7).

In the latter half of 1946, the United States Atomic Energy Commission released for investigative purposes, radioactive iodine of mass 131 (eight day half-life) from the atomic pile. The material became available to the authors in October 1946 and was used to assess its value in the therapy and diagnosis of toxic goiter. The latter part of the study was soon extended to a variety of clinical conditions in an attempt to evaluate the usefulness of this particular activity of the thyroid gland, iodine uptake, as an index of over-all thyroid function.

METHODS

Radioactive iodine, I^{131}, obtained from the Clinton Laboratories, Oak Ridge, Tennessee, was used throughout the study. Activity was deter-

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mined on receipt of the material, by means of a Geiger counter standardized according to the millicurie established by Marinelli from ionization chamber measurements at the Memorial Hospital (8). Variable standardization procedures are in use in different laboratories so that discrepancies of the order of 100 per cent may occur in estimating a millicurie of radioactive material and this factor must be taken into account in comparing the reports of different institutions. Tracer doses of I^{131} without significant amounts of stable iodine (carrier) were given by mouth in the nonfasting state. Doses of between 40 and 100 microcuries were used, the smaller

TABLE 1. RADIOIODINE UPTAKE IN EUTHYROIDISM

Per cent uptake at 24 hrs.	Control subjects
50–	—
40–49	2
35–39	4
30–34	8
20–29	24
10–19	18
0– 9	1

amount given being routinely in the later studies. Radioactivity in the thyroid gland was measured with a Geiger counter placed at a standard distance of 15 centimeters from the neck, with the thyroid isthmus as a center, and with the head and neck in a special holder. A wide counter aperture was designed which permits the accurate measurement of radiation from an area of the neck measuring 15×10 cm., sufficient for all except extremely large goiters. Measurements of uptake were made at the end of a 24-hour period. All patients were studied after complete medical work-up or after operation. No treatment was given prior to testing, except when mentioned.

RESULTS[1]

A. In control patients with euthyroidism.

Fifty-seven ward and clinic subjects with disorders not known to affect the endocrine system were studied (Table 1). Ages ranged from 16 to 72 years. There were 23 men and 34 women. Basal metabolic rates varied

[1] At present, the series includes about twice as many patients as when this article was submitted for publication. The observations reported in the various conditions are the same except for a larger number in each category.

widely, though the majority were within the range of plus 15 to minus 15 per cent and all patients were euthyroid clinically. The radioactive iodine uptake of the thyroid at 24 hours has a range of 7 to 49 per cent of the tracer dose. If a normal range of uptake is arbitrarily set with an upper limit of 35 per cent, 51 of the 57 cases, or 91 per cent are included. Six of the 57 cases, or 9 per cent are found above this range. If the upper limit is set at 40 per cent uptake, 2 in 57, or only 4 per cent of the cases exceed this point. The values exceeding the normal limits overlap with the lower levels of uptake found in toxic goiter, but the overlap is less for the 35 per cent limit, as will be seen subsequently.

TABLE 2. RADIOIODINE UPTAKE IN HYPERTHYROIDISM

Per cent uptake at 24 hrs.	Toxic diffuse goiter			Toxic nodular goiter
	Primary	Recurrent after treatment by		
		I^{131}	Surgery	
50–	48	9		
40–49	9	5	8	7
35–39	2	2	1	
30–34	1		1	
20–29	1	1		
10–19		2		
0–9				

In this group the effect of age is significant. One instance of uptake less than 10 per cent was noted in a normal subject aged 72. All but one of the uptakes in the lowest normal range of 10 to 15 per cent uptake, and the one uptake below 10 per cent just mentioned, occurred in women 40 years of age or more.

B. In hyperthyroidism.

1. Patients with active hyperthyroidism. A group of 97 cases of toxic goiter has been studied (Table 2). These have been divided into toxic diffuse and toxic nodular goiter. The former group has been subdivided into primary, or untreated cases and those that were recurrent despite therapy by either operation or radioctive iodine. A similar range of uptake is noted in all groups except in the one in which hyperthyroidism recurred after treatment with radioactive iodine. For the toxic group as a whole, 91

of the 97, or 94 per cent of the cases have uptakes exceeding 35 per cent. Six of the 97, or 6 per cent show uptakes not in excess of the normal range. In the primary group, only 2 cases, or 3 per cent, are within normal limits, whereas in the cases recurrent after radioactive iodine therapy, the incidence of uptake within the normal or even subnormal range is about five times as great (16 per cent). If the upper limit of normal is considered

TABLE 3. CORRELATION BETWEEN EXTREMES OF RADIOIODINE UPTAKE AND BASAL METABOLIC RATE IN EUTHYROIDISM AND HYPERTHYROIDISM

Thyroid status	Patient	B.M.R. %	Per cent uptake at 24 hrs.
			Greater than 35%
Euthyroid	Me.	+23	49
	O'to.	+ 3	43
	Pe.	+ 8	43
	Ke.	+15	39
	Fa.	−16	39
	Sa.	+20	36
	Ol.	+53*	36
			Less than 35%
Hyperthyroid	Sp.	+33	13
	Re.	+20	15
	Bl.	+50	19
	Ct.	+76	23
	Ma.	+24	34

* Could not obtain true B.M.R.

as 40 per cent uptake in order to include practically all control values, the number of toxic goiter cases falling within normal limits is increased to 11 in 97, or 11 per cent. There is, therefore, a significant and unavoidable overlap between control and hyperthyroid patients. A normal range with an upper limit of 35 per cent uptake permits 9 per cent of normal cases to be in the toxic range and 6 per cent of all toxic cases to be in the normal range (Tables 1, 2 and 3); whereas an upper limit of less than 40 per cent uptake alters these figures to 4 and 11 respectively. The individual data for the overlapping group, including basal metabolic rates, are presented in Table 3. The tables in this paper are divided to indicate a normal range of 10 to 35 per cent uptake.

2. Patients with remission of hyperthyroidism. The effect on radioactive iodine uptake of successful therapy for toxic goiter has been studied in 21 patients (Table 4). Remission followed either operation, cessation of antithyroid drug administration, external radiation with x-rays or internal

TABLE 4. RADIOIODINE UPTAKE IN REMISSION OF HYPERTHYROIDISM PRODUCED AFTER THERAPY

Per cent uptake at 24 hrs.	Surgery	Propyl-thiouracil	X-ray	I^{131}
50–				
40–49	1	1		4
35–39		1	1	
30–34				3
20–29	1	1		4
10–19				4
0–9				

radiation with radioiodine. It is clear that despite the return of the metabolic rate to normal, the iodine uptake often continues at an elevated level. Eight of the 21 cases in the series, or 38 per cent, have values in excess of the 35 per cent upper limit of normal uptake.

C. In miscellaneous thyroid disorders.

A variety of thyroid disorders other than toxic goiter have been surveyed by the tracer technique (Table 5). There are 44 cases in this group. The basal metabolic rates of these patients are normal, except for 1 instance of chronic thyroiditis and 3 of hypothyroidism.

1. Nontoxic goiter. The 3 patients with nontoxic diffuse goiter and 8 patients with nontoxic nodular goiter had normal basal metabolic rates

TABLE 5. RADIOIODINE UPTAKE IN VARIOUS THYROID DISORDERS

Per cent uptake at 24 hrs.	Nontoxic goiter		Malignant exoph-thalmos	Thyroiditis		Carcinoma	Hypo-thyroidism
	diffuse	nodular		acute	chronic		
50–			3*		1*		
40–49	1	1	1		1		
35–39	1	1			1		
30–34		2			2		
20–29		3	3		1	2	
10–19		1	1			5	
0–9	1			6	1	2	3

* 1 patient thyrotoxic.

and were clinically euthyroid. The same approximate distribution of uptake as in the control subjects was noted.

2. Malignant exophthalmos. This group consists of 8 instances of proven, or clinically suspected, malignant exophthalmos—7 patients in which the exophthalmos was present without a rise in basal metabolic rate, and 1 patient with an elevated basal metabolism. The radioiodine uptake of 2 of the 8 patients with normal metabolic rates exceeded the highest value for any control subject, and there is one other uptake greater than 40 per cent. The patient with definite thyroid overactivity also had a considerably elevated uptake.

3. Acute thyroiditis. The 6 cases in this group are of interest in view of the extremely low uptake of radioactive iodine in every instance, despite a normal basal metabolic rate. Follow-up measurements are not available in all, but there is a lag of one or more months until recovery of the uptake function occurs.

4. Chronic thyroiditis. The low uptake of iodine shown in acute thyroiditis is found in only 1 of the 7 chronic cases. The cases of Riedl's or of Hashimoto's struma have been combined in the table. A very low uptake may have diagnostic significance in differentiating these cases from carcinoma, providing the effect of age is also taken into account. More data are needed.

5. Carcinoma of the thyroid. Nine patients with untreated malignancy of the thyroid showed normal uptakes of iodine. In none of these had carcinoma entirely replaced the normal gland. Clinical information is missing in the 2 instances with uptakes of less than 10 per cent but these are suspected of having received previous therapy of some sort.

6. Hypothyroidism. The known low uptake of iodine in hypothyroidism (7) is confirmed in the 3 cases tested.

D. In pituitary and adrenal disorders

Nineteen examples of either eosinophile or chromophobe tumor of the anterior hypophysis have been studied (Table 6). The range of iodine uptake in the acromegalic group follows the normal pattern despite general but slight elevation of basal metabolic rate. In the chromophobe group the values hug the lower limits of normal or are below. Four outspoken and untreated instances of panhypopituitarism occur in this latter group. These patients had basal metabolic rates ranging from minus 17 to minus 41 per cent and levels of serum cholesterol (fasting) which ranged from 260 to 372 mg. per cent. However, 3 of the 4 showed uptake of radioactive iodine within the lower normal range.

Five instances of fairly advanced underfunction of the adrenal cortex *i.e.*, Addison's disease, were examined with the tracer technic in view of

TABLE 6. RADIOIODINE UPTAKE IN PITUITARY AND ADRENAL DISORDERS

Per cent uptake at 24 hrs.	Pituitary tumors		Adrenal disorders	
	eosinophile	chromophobe	Addison's disease	Cushing's syndrome
50–				
40–49	2			
35–39	1			
30–34	1		1	
20–29	2	1	1	
10–19	4	5	3	1
0–9		3		1

the low basal metabolic rate regularly found in this condition. The distribution of uptake is preponderantly in the low normal range. The uptake in the 2 instances of Cushing's disease, presumably, with adrenal cortical hyperfunction, is unusually low.

E. In nutritional disorders.

Eight patients with fairly extreme degrees of obesity and normal basal metabolic rates and 6 patients with anorexia nervosa (5 with low basal metabolisms of minus 21 to minus 30 per cent), were examined (Table 7). The uptake in all was within normal limits except for 1 instance of obesity. The lack of correlation between basal metabolic rate and uptake of I^{131} is emphasized in the anorexia nervosa group. The obese patient with the low uptake had diarrhea at the time of the test and may have failed to absorb much of the radioactive iodine from the gut.

TABLE 7. RADIOIODINE UPTAKE IN NUTRITIONAL DISTURBANCES

Per cent uptake at 24 hrs.	Obesity	Anorexia nervosa
40–49		
35–39		1
30–34	3	1
20–29	3	1
10–19	1	3
0–9	1	

F. In miscellaneous endocrine disorders.

Single examples of several endocrine disorders other than those listed above have been tested in pilot experiments. No significant deviation from normal uptake was noted.

Effect of preceding administration of desiccated thyroid or of stable iodine

The tracer uptakes by the thyroid gland of 4 euthyroid patients, during and after the administration of desiccated thyroid, are presented in Table 8. The striking depression of uptake during therapy and the occasional long delay in recovery after discontinuance are clearly shown. As little as 0.12 Gm. of desiccated thyroid by mouth may cause a depression of uptake to 4 per cent of the tracer dose, *i.e.*, to the hypothyroid range. In the case in which uptake failed to return to normal within ten weeks after omission of the drug, the patient denied its resumption and there was no reason to suspect her veracity.

Six cases previously given stable iodine were studied at varying intervals after the last administration of the drug. The first 4 patients listed had received sodium or potassium iodide for several weeks to several months; patient M.C. had had a single intravenous injection of Diodrast to outline an obstructed brachial vein, and patient J. S. had been given diiodophenolphthalein, for an intravenous pyelogram. The known depression of uptake after iodine administration is confirmed (9). Recovery is seen to be delayed in all but S.M. (in whom uptake was high in the fourth week off iodine) and in M.C. where only four days had elapsed to the time of the tracer test. In one patient, M.F., recovery is still greatly delayed seven weeks after cessation of therapy. Again, there is no reason to doubt the reliability of the subject in his statement that he had had no further iodine. The data in patient L. S. are complicated by the fact that propylthiouracil was taken intermittently during the twelve weeks since omission of iodine. This medication was stopped four weeks before the tracer test, which reveals a zero uptake.

DISCUSSION AND CONCLUSIONS

A fact-finding survey of the uptake of tracer doses of radioactive iodine I^{131}, has been made in conditions of normal and disordered thyroid function in man. Direct measurement of the uptake by the thyroid gland has been determined as described in a previous publication (6). This method was decided upon as more accurate and feasible than the determination of the urinary excretion of radioactive iodine. There is a reciprocal relationship between uptake by the gland and excretion in the urine (10). The sum of uptake by the thyroid gland and excretion in the urine accounts for from 60 to 80 per cent of the administered iodine, the rest being distributed

TABLE 8. EFFECT OF PRECEDING ADMINISTRATION OF DESICCATED THYROID OR OF STABLE IODINE ON RADIOIODINE UPTAKE

Desiccated thyroid group					
Patient	Daily dose Gm.	Weeks since thyroid omitted	B.M.R. %	Cholesterol	Per cent uptake at 24 hrs.
C.B.	0.3	0 8	+ 5 −15	150 204	4 26
P.O.B.	0.24	0 7	+ 6 −17	120 168	2 24
F.W.	0.12	0 6	−12 −13	195 201	4 3
R.B.	not known	10	+ 1	184	4
Stable iodine group					
Patient	Daily dose Gm.	Weeks since iodine omitted	B.M.R. %	Cholesterol	Per cent uptake at 24 hrs.
M.F.	iodide by mouth	1½ 7	+69	195	2 2
R.F.	iodide by mouth	4	+23	208	8
S.M.	iodide by mouth	4	−12	197	46
LS.	iodide by mouth	12	+45	288	0
M.C.	Diodrast	½	± 0		10
J.S.	I.V. pyelogram	2 4			3 4

throughout the body. Mathematical treatment of the data from urine studies may well reflect gland uptake. However, apart from the inherent possibility of inaccuracy from indirect methods, the danger of mistakes in the collection of urine, known or unknown to the physician, tends to rule out this method for routine clinical use.

There is little doubt at present that accurate direct measurement of the

iodine uptake by the gland is feasible (6). Errors in determination may result when the dimensions of the gland exceed those measurable by a given Geiger counter aperture. A large counter with a wide aperture at some distance from the neck can be designed to cover an area wide enough for almost every type of gland. Such an arrangement is not useful for localization within, or measurement of uptake in part of the gland. A small counter placed directly against the neck is suitable for this latter purpose but is subject to error if used for over-all uptake measurement. By means of the Geiger counter, iodine uptake by the gland can be expressed in terms of the percentage of a tracer dose collected at a given time interval or as the rate of accumulation during a given period (11).

The present study is based on the determination of the percentage uptake of the radioiodine at 24 hours after ingestion, at which point uptake has become stabilized (6) and significant excretion has not begun except in rare instances of toxic goiter. Only one determination is necessary and the method is convenient for routine clinical practice.

The diagnostic usefulness of this technic has needed documentation. In the controls studied, a range of uptake of between 10 and 35 per cent of the tracer dose at 24 hours has been found to include all but 9 per cent of cases. The significance of such limits of normal uptake requires evaluation.

Most of the low values between 10 and 15 per cent, and a single value of below 10 per cent were, found in women over 40 years of age. This physiologic decrease in uptake has been found by Perlmutter (12) in both sexes, accompanied by normal plasma precipitable iodine levels. Thus, the proposition of decreased thyroid function based on low tracer uptake values must take into account the effect of aging.

High uptake values at the upper range of normal or above also require interpretation. A 35 or 40 per cent uptake limit permits an appreciable percentage of cases of proven toxic goiter to be included in the normal range. This same overlap is found when the "accumulation gradient" is determined and occurs with plasma precipitable iodine and basal metabolic rate determinations. A more precise method may have been found in the more recent technic proposed by Stanley and Astwood (13), although it has as yet been applied only to the study of the effectiveness of antithyroid drugs, and has not been used to determine whether it will narrow the percentage overlap between normal and toxic goiter patients.

The degree of correlation of radioiodine uptake with the basal metabolic rate in conditions other than toxic goiter is also of great interest. While unquestionably there is a general relationship, lack of correlation is not infrequent. Thus, after unsuccessful or successful therapy for toxic goiter in malignant exophthalmos, acute and occasionally chronic thyroiditis, pituitary and adrenal disorders, anorexia nervosa, and following the ad-

ministration of thyroid substance containing stable iodine, there may be a distinct discrepancy between iodine uptake and basal metabolic rate. In these patients, the basal metabolic rate appears to be markedly altered without detectable change in thyroid function as indicated by radioiodine uptake. Explanation for this may be found in one of several hypotheses: in an inherent ability of tissues to change their rate of metabolic activity in the face of a constant thyroid hormone blood level; in a dissociation between inorganic iodine uptake and a subsequent hormone release by the gland, such as is seen with antithyroid drug administration; or in present inability to interpret the significance of minor, or temporary, degrees of change in iodine uptake and in plasma bound iodine, especially since there is generally no preceding baseline of uptake to cover the period when the individual was healthy, or no adequate history in respect to possible preceding iodine intake such as with iodized salt or medicinal iodides. Further study will be necessary before one of these, or another reason can be accepted.

The effect of large doses of desiccated thyroid in causing a reduction of thyroid activity is now well known (14, 15). The minimal dose of desiccated thyroid which will accomplish this result and the fact that almost complete suppression of uptake may exist for weeks after cessation of therapy in some people, is not so well appreciated. The extensive use of desiccated thyroid by the gynecologist for the treatment of menstrual and sterility difficulties, and by many other physicians for the treatment of obesity, should perhaps be subjected to consideration from this standpoint. The occasional low plasma iodine levels in obesity reported by Williams (16) may be possibly explained by the use of thyroid at some period shortly before the determinations.

Stable iodine too, has been recognized as capable of reducing iodine uptake by the gland. Again, the long duration of the suppression response and the discrepancy from the normal basal metabolic rate are brought out in this study and are of importance from the standpoint of mechanisms involved and in the clinical application of the tracer test.

From the findings we have demonstrated, it can be seen that the radioactive iodine tracer test, when used as a clinical tool for determination of thyroid function, has diagnostic usefulness only when the results are properly interpreted in conjunction with other clinical and laboratory aids. It has not replaced sound clinical judgment.

SUMMARY

1. The uptake of a tracer dose of I^{131} by the thyroid gland has been measured by means of a Geiger counter, directly over and 15 centimeters

away from the gland, in normal subjects and in patients in whom a knowledge of thyroid function might be of interest.

2. The normal range of uptake is between 10 per cent and 35–40 per cent of the administered dose, at 24 hours.

3. There is a small but significant overlap of uptake between the control subjects and patients with toxic goiter.

4. In cases of toxic goiter, the general correlation which exists between iodine uptake by the thyroid gland, and hormone secretion as reflected by the basal metabolic rate, can be disrupted by the treatment of the thyrotoxicosis.

5. Lack of correlation between iodine uptake and basal metabolism may be found in active thyroiditis, malignant exophthalmos, Simmonds' disease, Addison's disease and anorexia nervosa.

6. The depression of iodine uptake by previously administered thyroid substance or stable iodine may persist for weeks.

REFERENCES

1. Hamilton, J. G., and Soley, M. H.: Studies in iodine metabolism by the use of a new radioactive isotope of iodine, *Am. J. Physiol.* **127:** 557, 1939.
2. Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive iodine as an indicator in the study of thyroid physiology, *Proc. Soc. Exper. Biol. & Med.* **38:** 510, 1938.
3. Livingood, J. J., and Seaborg, G. T.: Radioactive isotopes of iodine, *Physiol. Rev.* **54:** 775, 1938.
4. Hertz, S., and Roberts, A.: Radioactive iodine in the study of thyroid physiology. VII. The use of radioactive iodine therapy in hyperthyroidism, *J.A.M.A.* **131:** 81, 1946.
5. Miller, E. R.; Soley, M. H., and Dailey, M. E.: Preliminary report on the clinical use of radioactive I^{131}, *Am. J. Roentgenol.* **60:** 45, 1948.
6. Werner, S. C.; Quimby, E. H., and Schmidt, C.: Clinical experience in diagnosis and treatment of thyroid disorders with radioactive iodine (eight day half life), *Radiology* **51:** 564, 1948.
7. Hamilton, J. G., and Soley, M.: Studies in iodine metabolism of the thyroid gland in situ by the use of radio-iodine in normal subjects and in patients with various types of goiter, *Am. J. Physiol.* **131:** 135, 1940.
8. Marinelli, L. D.; Quimby, E. H., and Hine, G. J.: Dosage determination with radioactive isotopes. II. Practical considerations in therapy and protection, *Am. J. Roentgenol.* **59:** 260, 1948.
9. Morton, M. E.: Charkoff, J. L., and Rosenfeld, S.: Inhibiting effect of inorganic iodine on the formation in vitro of thyroxine and diiodotyrosine by surviving thyroid tissue, *J. Biol. Chem.* **154:** 381, 1944.
10. Keating, F. R.; Power, M. H.; Berkson, J., and Haines, S. F.: The urinary excretion of radioiodine in various thyroid states, *J. Clin. Investigation* **26:** 1138, 1947.
11. Stanley, M. M., and Astwood, E. B.: Determination of the relative activities of antithyroid compounds in man using radioactive iodine, *Endocrinology* **41:** 66–84 (July) 1947.
12. Perlmutter, M.: Thyroid activity in senescence and hypometabolic states; as-

sayed by determination of thyroid uptake of radioactive iodine and protein bound iodine of blood. To be published.

13. Stanley, M. M., and Astwood, E. B.: The accumulation of radioactive iodide by the thyroid gland in normal and thyrotoxic subjects and the effect of thiocyanate on its discharge, *Endocrinology* **42**: 107–123 (Feb.) 1948.
14. Uotila, U. U.: The regulation of thyrotropic function by thyroxin after pituitary stalk section, *Endocrinology* **26**: 129–135 (Jan.) 1940.
15. Riggs, D. S.; Man, E. B., and Winkler, A. W.: Serum iodine of euthyroid subjects treated with desiccated thyroid, *J. Clin. Investigation* **24**: 722, 1945.
16. Williams, R. H.: Relation of obesity to the function of the thyroid gland, especially as indicated by the protein-bound iodine concentration in the plasma, *J. Clin. Endocrinol.* **8**: 257–261 (March) 1948.

ANTIHORMONE FORMATION COMPLICATING PITUITARY GONADOTROPIN THERAPY IN INFERTILE MEN

II. EFFECT ON NUMBER OF SPERM, MORPHOLOGY OF THE TESTIS AND URINARY GONADOTROPINS*

EDWIN C. JUNGCK, M.D., PH.D.,**† WILLIAM O. MADDOCK, M.D., PH.D.,† CARL G. HELLER, M.D., PH.D., AND WARREN O. NELSON, PH.D.

Departments of Physiology and Medicine, University of Oregon Medical School, Portland Oregon, and the Department of Anatomy, State University of Iowa College of Medicine, Iowa City, Iowa

THE search for therapeutic agents effective in male infertility has been relatively fruitless to date. In recent years, hormonal therapy has been considered. Of the various hormones, the ones most likely to succeed would seem to be those that ordinarily stimulate spermatogenesis: the gonadotropins. Of the gonadotropins (from anterior pituitary, pregnancy urine and pregnant mare serum sources), one hormone that is known specifically to stimulate spermatogenesis is follicle-stimulating hormone (FSH) of the anterior pituitary (1).

It cannot be expected that FSH will prove effective in all types of male sterility. Several prerequisites are necessary before successful results can reasonably be expected. In addition to the obvious prerequisites, such as patent vas deferens, and the knowledge that the wife is potentially capable of conceiving, we have considered the following conditions to be essential:

1. *Testes with potentially reversible defects.* In many cases of infertility, the testes are irreparably damaged and attempts at therapy of any kind are useless.

2. *Gonadotropin production that is not already elevated.* If there were already an increase in endogenous gonadotropic hormones, adding FSH from an exogenous source could not be expected to stimulate spermatogenesis.

Hypogonadotropic eunuchoid men are good examples of patients meeting both these requirements, for they have infantile testes capable of responding to gonadotropic stimulation, and *subnormal* gonadotropin titers. Administration of FSH to such patients, following treatment with chorionic

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gonadotropin, will produce complete spermatogenesis (2).

3. *A suitably concentrated source of FSH.*

In studying over 100 infertile men with the view of determining whether prerequisites 1 and 2 were met, it was found that the majority were eliminated because of 1) irreparable testicular damage, and/or 2) elevation of gonadotropins. In the current investigation, 7 infertile, but otherwise normal men were chosen who had either normal or low urinary gonado-

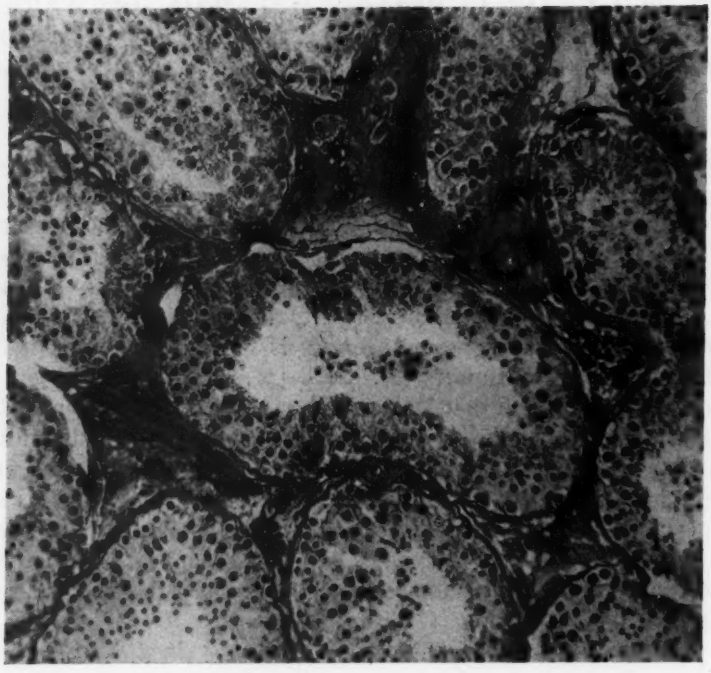

FIG. 1a. Biopsy specimen of testis from patient K. H. *before therapy*, showing seminiferous tubules of approximately normal size containing all stages of spermatogenesis, but a relative preponderance of the more immature stages, and sloughing of immature forms into the lumen of the tubules. There is a cluster of normal-appearing Leydig cells near top center. Note lack of any irreversible changes such as severe or complete hyalinization of the basement membrane. ×175.

tropin excretion and in whom biopsies of the testis revealed minor, but definite alterations in spermatogenesis. The third prerequisite was met when a potent and partially purified hypophyseal extract from sheep, containing predominantly FSH, was made available to us.[1] Details concerning

[1] Generously supplied by the Schering Corporation through the courtesy of Dr. Edward Henderson.

treatment are presented graphically in Figures 3 to 8, and are recorded in Table 2 of the preceding report (3).

In the preceding report (3), it was demonstrated that the administration of sheep FSH elicited formation of antihormones that were capable of neutralizing the patients' endogenous gonadotropic hormones. It is the purpose of this communication to correlate the effects of sheep FSH and

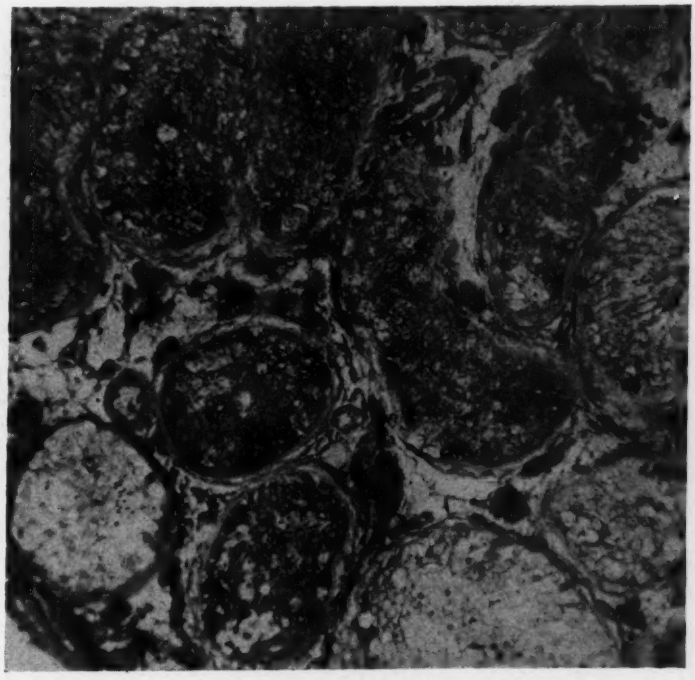

FIG. 1b. Biopsy specimen of testis from K. H. *during antihormone formation.* There is a striking decrease in the size of the seminiferous tubules as compared with the specimen obtained before treatment. Mature germinal cells are scarce, leaving a preponderance of spermatogonia and primary spermatocytes. Tubules are completely filled by immature cells sloughing into the lumens. Spermatozoa are present; however, these are deep-staining and seemingly are old, retained sperm. Note the lack of any recognizable Leydig cells. The appearance is similar to that occurring in pituitary failure in the human adult or in hypophysectomized animals. × 175.

subsequent antihormone formation on spermatogenesis and endogenous gonadotropin excretion.

RESULTS

Morphology of the testes. Biopsy specimens of the testis were obtained from 6 of the 7 men before initiating therapy. (The seventh patient was

included because he was found to have subnormal titers of urinary gonadotropins.) The principal defects encountered were disorganization of spermatogenesis, lack of maturation, and sloughing of immature germinal cells into the lumen of the seminiferous tubules. There was a lack of irreversible changes such as severe or complete hyalinization of the basement membrane of the seminiferous tubules or lack of all germinal cells. The

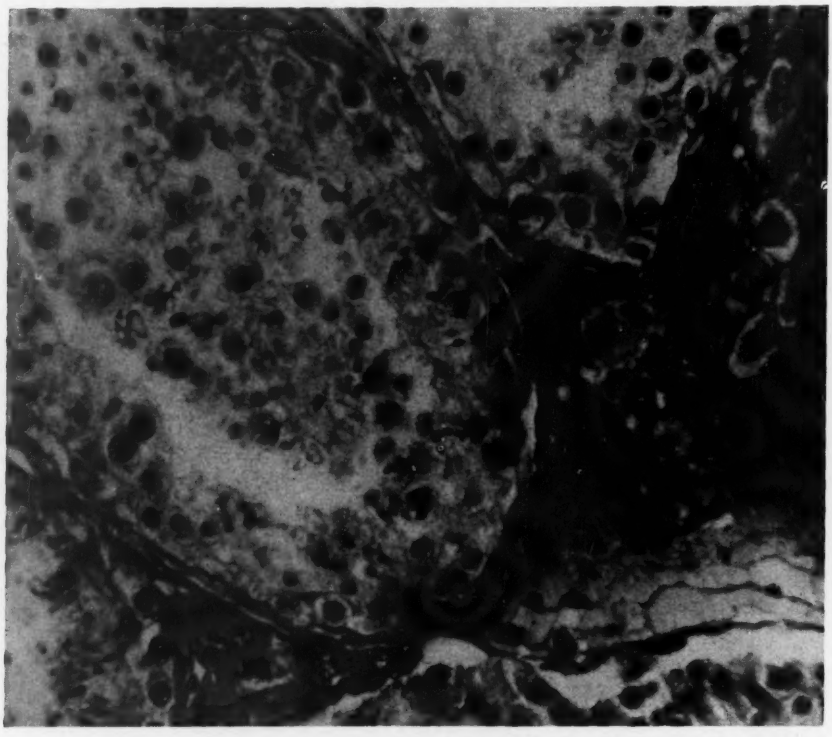

FIG. 2a. Biopsy specimen of testis from patient K. H. *before therapy:* upper left area of Figure 1a, × 450. Note that all stages of spermatogenesis are represented and that normal-appearing Leydig cells are present.

encouraging feature was the presence of germinal cells in various stages of maturation which seemingly could go on to sperm formation with the proper impetus. The Leydig cells appeared normal, which was in accord with lack of any clinical evidence of androgen deficiency. The biopsies showed a marked similarity; a representative biopsy specimen (patient K. H.) is illustrated in Figures 1a and 2a.

Sperm counts. Sperm counts were performed by diluting seminal fluid

in a red or white cell pipette with dilute aqueous methylene blue, and then counting the sperm in a Neubauer counting chamber. Sperm counts are presented graphically in Figures 3 to 8. (As no more than an occasional

FIG. 2b. Biopsy specimen of testis from patient K. H. *during antihormone formation:* lower left area of Figure 1b, × 450. Note that spermatogenesis has ceased at the primary spermatocyte stage, and that dark-staining sperm are retained in the tubules. Small cells with pyknotic nuclei are present in the two right-hand tubules. Leydig cells are not seen.

sperm was encountered in R.C.'s specimens, data on his sperm counts are not presented.) Although abnormalities in sperm morphology and motility were observed in some of the patients, no significant alterations occurred during or after therapy.

Great variations in the number of sperm were observed before, during

and after instituting therapy. Averages before, during and after therapy, however, indicated an upward trend during FSH therapy in the 6 patients, followed by a decrease during the time of maximal antihormone formation in 3 of the patients with high antihormone titers. The decrease in each instance was below the pretreatment average number of sperm. A fourth patient with similarly high antihormone titers also had a decrease in number of sperm during the time antihormones were elevated, but the onset of the decrease was delayed until two and one half months after initial antihormone detection. The 2 patients in whom numbers of sperm did not decrease experienced the least amount and shortest duration of antihormone formation.

Following the disappearance of detectable antihormones in the plasma, the average number of sperm rose to pretreatment levels or higher in the 3 cases in which a decrease had occurred, and remained at the pretreatment level or higher in the 2 in which no decrease was encountered. The patient with the delayed decrease continued to have a low sperm count, and continued to have antihormones in the plasma at the last date tested, 283 days after stopping therapy.

Urinary gonadotropin excretion:

Before treatment was instituted, gonadotropin titers were normal in 5 patients, below normal in 1 and at the upper limits of normal in 1 (Table 1). Figures for normal individuals are presented in a previous publication (4).

During FSH administration (5 patients tested) no increase in gonadotropin excretion was noted. The titers fell below the pretreatment level in 4 patients and remained unchanged in 1 (Table 1).

After FSH administration had been stopped, and during the time of antihormone formation, gonadotropin excretion was increased to the pretreatment level in 6 patients and was slightly above the pretreatment level in the remaining 1 (Table 1).

After or at about the time of disappearance of antihormones from the circulation, gonadotropin excretion was above the pretreatment level in 3 patients and equal to the pretreatment level in 3 others (Table 1).

DISCUSSION

Sperm Counts. Following the initiation of FSH therapy, there was an initial rise in the sperm output that soon reached a plateau, or sharply declined to levels that were in some instances lower than before therapy was begun. With the exception of 1 patient, the rise in output of sperm was slight. There was no improvement in the impaired motility or the abnormal

TABLE 1. URINARY GONADOTROPIN ASSAYS BEFORE, DURING AND AFTER FSH THERAPY AND ANTIHORMONE FORMATION

Patient	Anti-hormone formation	Relation to FSH administration	Time elapsing between initiation of therapy and collection of urine (days)	Assay rats*		
				Uterine weight mg.	Ovarian weight mg.	Number of rats
D.B.	0	Before	0	47	11	7
	+	After	65–68	56	10	4
	0	After	185–188	110	12	4
H.B.	0	Before	0	108	21	7
	+	During	66–69	58	9	4
	+	During	101–104	130	12	4
	+	After	141–146	115	22	3
	0	After	241–244	141	26	4
R.C.	0	Before	0	63	28	8
	0	During	45–49	90	13	4
	+	During	81–84	78	14	4
	+	After	87–92	59	13	3
	+	After	138–147	86	12	3
	0	After	200–203	84	44	3
L.D.	0	Before	0	123	23	8
	+	During	63–66	76	10	4
	+	After	83–88	173	22	3
	+	After	179–184	107	69	3
C.G.	0	Before	0	118	38	4
	+	After	64–67	135	16	2
	+	After	96–99	101	51	2
	+	After	167–172	126	45	4
	+	After	186–191	109	24	3
	+	After	249–253	100	64	3
	+	After	282–288	89	77	3
K.H.	0	Before	0	120	12	4
	+	During	64–66	36	8	3
	+	After	69–72	41	8	4
	+	After	73–76	113	12	2
	+	After	185–190	125	23	3
	+	After	218–221	120	18	4
G.M.	0	Before	0	72	18	7
	0	During	26–29	92	19	4
	+	During	54–56	133	23	4
	+	After	71–76	116	25	3
	+	After	162–168	125	17	4
Uninjected control rats				36	13	63

* Each rat received the ultrafilter concentrate of a 12-hour urine specimen.

morphology of the sperm encountered in some of the patients. The lack of decided improvement, despite the fact that the 7 subjects seemed suitable candidates for FSH therapy, may be due to 1) insufficient amounts of FSH administered, 2) the formation of antihormones which interfered so early that the time allowed for stimulating spermatogenesis may have been inadequate, or 3) the defects in spermatogenesis may not have been amenable to correction with gonadotropins.

The slight rise in average numbers of sperm occurring in 5 patients and the sharp rise in 1 lend encouragement to the possibility that FSH therapy

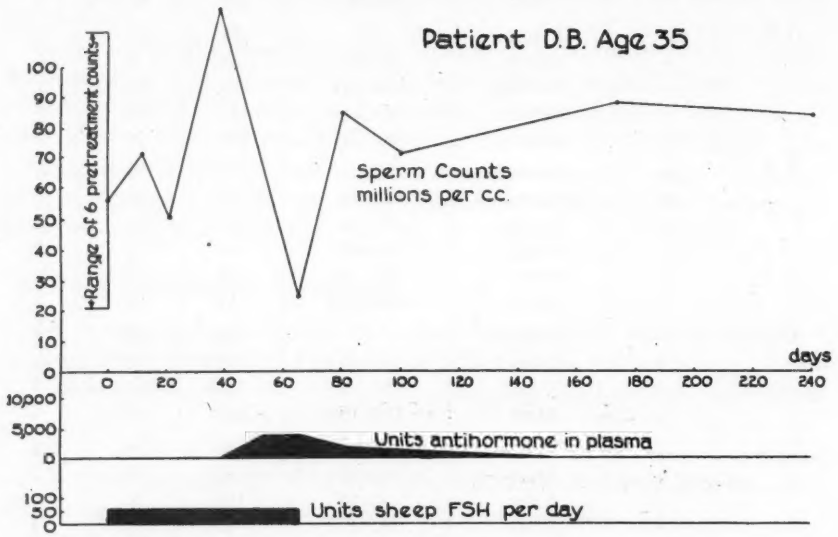

FIG. 3

is potentially capable of stimulating spermatogenesis. The fact that an early plateau or early decline occurred could be correlated with the presence of antihormones in most instances. Thus, one limiting factor in adequate therapy appears to be the formation of antihormones. To circumvent early antihormone formation, perhaps other sources of gonadotropins or more highly purified forms of FSH, less apt to elicit antihormone formation (5), could be applied.

It would appear that antihormone formation did not cause permanent suppression of spermatogenesis, since output of sperm increased to pretreatment levels or above after the antihormones disappeared from the circulation.

The effects of antihormone formation on the microscopic appearance of

the testis were studied in two instances in which biopsies were repeated after therapy when antihormones were present. In patient C.G., the tissue was removed for biopsy on day 179, and in patient K. H., on day 67 after initiating therapy. In both patients, sperm counts were decreasing at the time the biopsy specimen was obtained.

Similar changes occurred in both patients and consisted of a reduction in size of the seminiferous tubules, reduction in the number of mature cells of the germinal series leaving a preponderance of spermatogonia and primary spermatocytes, sloughing of a large number of immature cells into

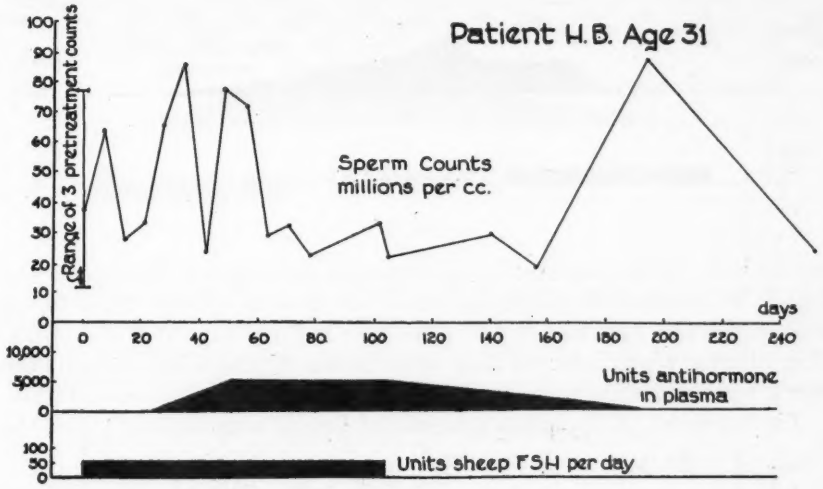

FIG. 4

the lumen of the tubules, an apparent retention of mature spermatozoa (which stained deeply and seemingly were old forms), and disappearance of recognizable interstitial cells of Leydig (Figures 1 b and 2 b, patient K. H.). The general appearance was similar to that encountered in pituitary failure in the human adult (6). The appearance was not unlike that seen in adult hypophysectomized animals (7).

The obvious explanation for the marked regression of the seminiferous tubules is that the antihormones prevented stimulation of the tubules by either the exogenous sheep FSH or the patients' endogenous FSH. Thus, as concerns the seminiferous tubules, the patient had been essentially hypophysectomized.

As judged by the biopsy of the testis, spermatogenesis appeared to have ceased, yet the seminal fluid contained sperm. The capacity of the epididy-

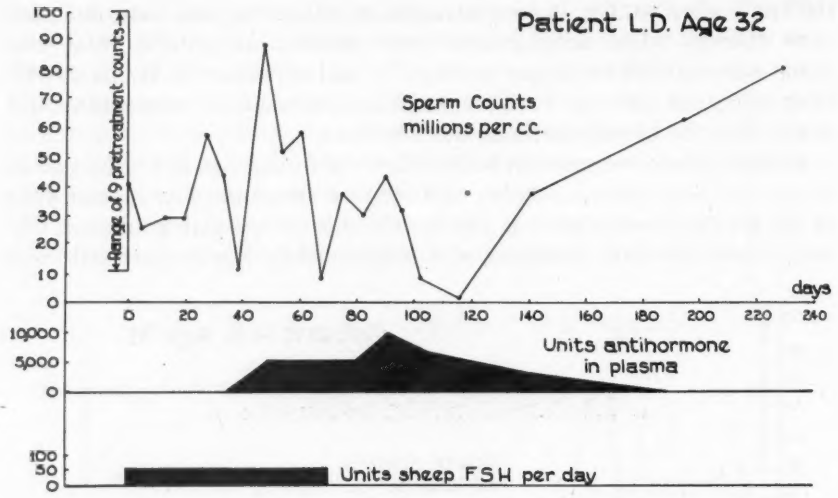

FIG. 5

mis to store sperm may explain this apparent discrepancy. Hammond and Asdell (8) isolated the epididymis from the testis in rabbits. They found that the rabbits remained fertile for as long as forty days after the operation (during which interval they were mated 6 times) and that motile sperm remained in the epididymis for as long as sixty days after operation.

The regression of the interstitial cells of Leydig suggests that either the

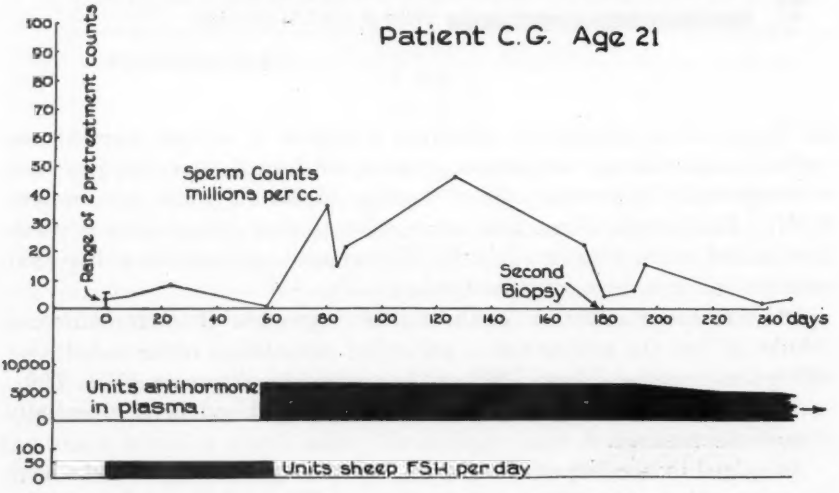

FIG. 6

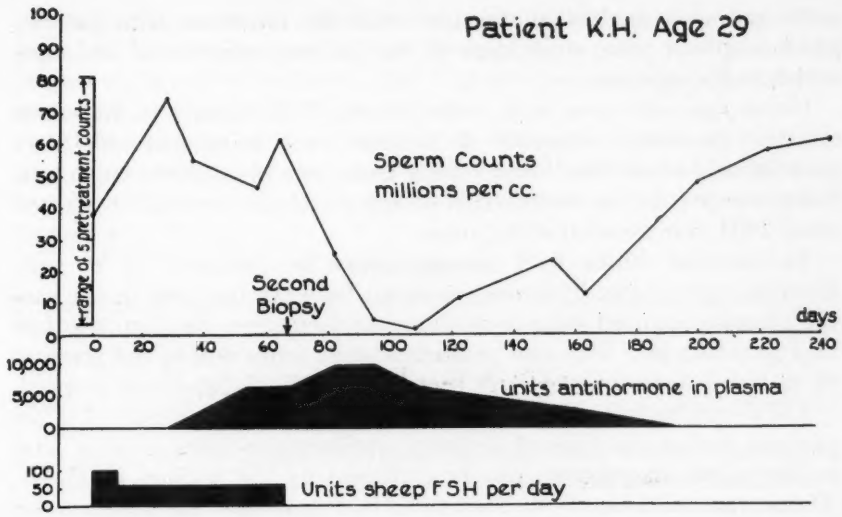

FIG. 7

sheep FSH contained enough interstitial-cell stimulating hormone (ICSH) to cause anti-ICSH formation, thus preventing stimulation of the Leydig cells by endogenous ICSH; or the antihormones to FSH were sufficiently non-hormone-specific to prevent endogenous ICSH stimulation. Appar-

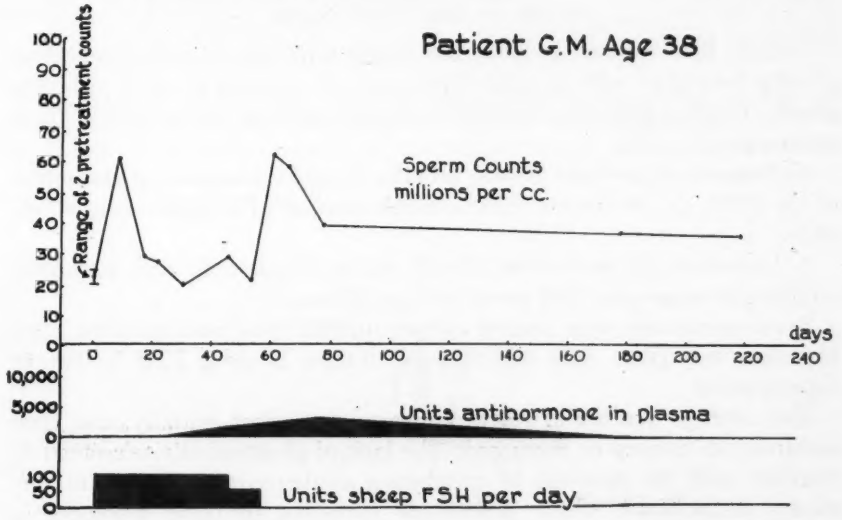

FIG. 8

ently androgen production was not markedly interfered with for any great length of time; since none of the patients experienced androgen withdrawal symptoms.

Urinary gonadotropins were tested during FSH therapy to determine whether appreciable amounts of hormone were being excreted. Since gonadotropic titers were lower during treatment than before treatment, it seems reasonable to conclude that no appreciable amounts of the injected sheep FSH were excreted in the urine.

The decrease during FSH therapy cannot be accounted for by antihormone suppression. This was concluded from the fact that in one case the decrease occurred prior to antihormone formation, and from the fact that gonadotropins increased to pretreatment levels during the presence of maximal antihormone titers soon after FSH therapy was stopped.

The rise in the level of gonadotropins which was encountered in 4 of the patients during the time of declining antihormone titers or soon after antihormones disappeared, can be explained by the findings of Meyer, Kupperman and Finerty (9). They noted that upon injecting antihormones into rats, a rise in the pituitary content of gonadotropins occurred. Upon stopping the injections of antihormones, evidence of increased secretion of gonadotropin was obtained, following which the gonadotropin content of the pituitary decreased. They concluded that the increased pituitary secretion of gonadotropins was due to the decrease in gonadal function caused by administering antihormones.

SUMMARY AND CONCLUSIONS

Criteria have been set forth for the selection of candidates for treatment of male infertility with a purified preparation of sheep anterior pituitary glands containing mainly follicle-stimulating hormone (sheep FSH). These criteria require that:

1. Biopsies of the testis should reveal a suitable substrate for the action of the FSH, *i.e.*, testicular defects should appear to be potentially reversible.

2. Gonadotropin production should not be elevated. In such instances, addition of exogenous FSH would be superfluous.

Seven sterile men were judged to have fulfilled these prerequisites. They therefore were given daily injections of 50 units of sheep FSH for two to three months.

The average number of sperm increased somewhat initially, and then remained stationary or decreased. The lack of progressive rise seemed to coincide with the presence of circulating antihormones; as the antihormones disappeared, sperm production increased in those instances in which it had formerly declined.

Biopsy specimens of the testis from 2 patients, taken at a time when antihormones were present and when sperm counts were decreasing, revealed a microscopic appearance not unlike that encountered following hypophysectomy in adult animals.

Urinary gonadotropin excretion was determined before, during and after therapy. The injected sheep FSH was not excreted in the urine in appreciable quantities. Antihormones did not suppress endogenous gonadotropin excretion.

REFERENCES

1. Greep, R. O.; van Dyke, H. B., and Chow, B. F.: Gonadotropins of the swine pituitary. I. Various biological effects of purified thylakentrin (FSH) and pure metakentrin (ICSH), *Endocrinology* **30:** 635–649 (May) 1942.
2. Heller, C. G., and Nelson, W. O.: Classification of male hypogonadism and a discussion of the pathologic physiology, diagnosis and treatment, *J. Clin. Endocrinol.* **8:** 345–366 (May) 1948.
3. Maddock, W. O.: Antihormone formation complicating pituitary gonadotropin therapy in infertile men. I. Properties of the antihormones, *J. Clin. Endocrinol.* **9:** 213–233 (March) 1949.
4. Jungck, E. C.; Maddock, W. O., and Heller, C. G.: Gonadotropic hormone: comparison of ultrafiltration and alcohol-precipitation methods of recovery from urine, *J. Clin. Endocrinol.* **7:** 1–10 (Jan.) 1947.
5. Leathem, J. A., and Abarbanel, A. R.: Purification of equine gonadotropin and its effect on the appearance of antigonadotropic substances in human sera, *J. Clin. Endocrinol.* **3:** 206–211 (April) 1943.
6. McCullagh, E. P.: Testicular dysfunction; some clinical aspects. Presented before the New York Academy of Medicine, Oct. 16, 1947.
7. Smith, P. E.: Maintenance and restoration of spermatogenesis in hypophysectomized rhesus monkeys by androgen administration, *Yale J. Biol. and Med.* **17:** 281–287 (Oct.) 1944.
8. Hammond, J., and Asdell, S. A.: The vitality of the spermatozoa in the male and female reproductive tracts, *Brit. J. Exper. Biol.* **4:** 155–185 (Dec.) 1926.
9. Meyer, R. K.; Kupperman, H. S., and Finerty, J. C.: Increase in gonadotropic content of pituitary glands of female rats treated with antigonadotropic serum, *Endocrinology* **30:** 662–666 (May) 1942.

THE RELATIVE INDEPENDENCE OF SODIUM AND CHLORIDE EXCRETION*

JOSEPH W. GOLDZIEHER, M.D. AND GILBERT C. H. STONE, PH.D.

From the Research Division and Endocrine Clinic, St. Clare's Hospital, New York and the Department of Chemistry, The City College of New York

IN THE early days of electrolyte studies, the concept of "salt" (*i.e.*, sodium chloride) metabolism was widely used. This is exemplified by Zondek's "salt-and-water obesity," a study which was based entirely on chloride determinations (1). Since that time it has been noted that sodium and chloride levels do not always follow a parallel course. In shock and in alkalosis, profound changes in blood chlorides occur with relatively little alteration of the sodium level. In cases of adrenal tumor, low plasma chlorides have been associated with high (2) or normal (3) plasma sodium values. Differences between the urinary excretion of sodium and chloride have been observed very recently in cardiac edema and in hepatic cirrhosis (4). Nevertheless, the habit of judging sodium metabolism by chloride values, and the expression of chloride concentrations as "milligram per cent of sodium chloride" or chloride output "as sodium chloride" persists. Extensive work on the relation of steroid hormones to electrolyte balance, as well as renewed interest in sodium metabolism as related to heart failure and hypertension, have emphasized the need for separate evaluation of sodium and chloride balance. With the availability of a simple method for the determination of sodium in biologic fluids, simultaneous balance studies of sodium and chloride were carried out to determine how frequently these substances are treated by the body in parallel fashion.

MATERIALS AND METHODS

Fifty consecutive patients referred for endocrine investigation of various problems were studied. This potentially abnormal material was selected purposely because of the greater likelihood and importance of finding irregularities of electrolyte metabolism. The patients were maintained on identical diet and fluid intakes for two consecutive days during which 24-hour urine samples were collected. The first day was taken as a control, and on the second day 10 Gm. (0.188 mol) of sodium chloride in gelatin capsules and 250 cc. of water were given between 9 and 10 a.m. Total sodium excretion was determined by the method of Goldzieher and Stone

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* Read by title before the Thirtieth Annual Meeting of the Society for the Study of Internal Secretions, Chicago, Illinois, June 18 and 19, 1948.

(6) and total chloride by the method of Schales and Schales (7, 8). From these data, the percentage excretion of the test sodium and chloride could be calculated.

RESULTS

The data obtained are shown as a scatter diagram in Figure 1, the retention of the test sodium being plotted as the abscissa, and the retention of the test chloride as the ordinate. It is usually assumed that with equal

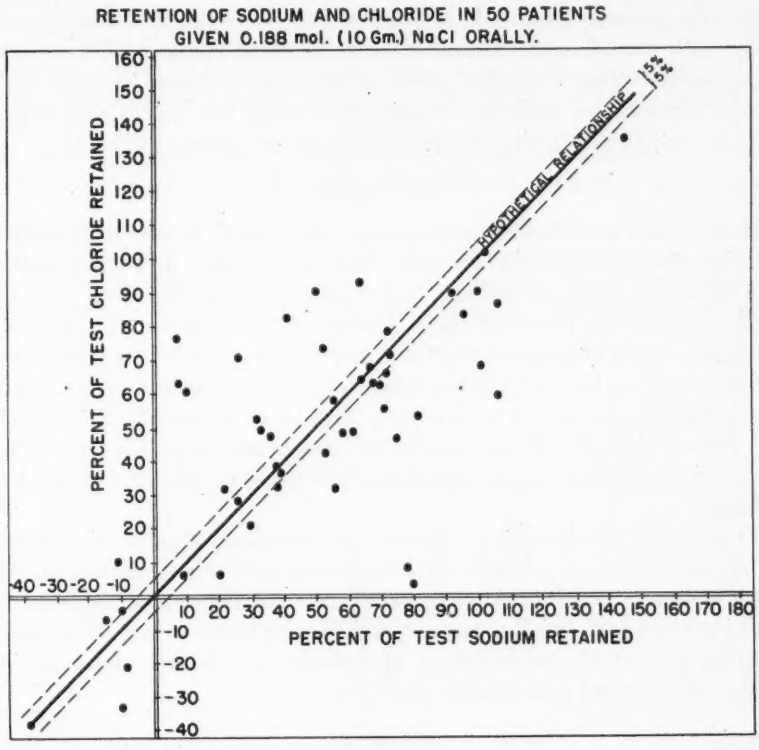

FIG. 1

amounts of sodium and chloride ingested, the percentage retention or excretion of one should be essentially identical with the percentage retention or excretion of the other. This hypothetical situation would yield a series of values which form a straight-line relationship, as illustrated. It is found, however, that very few of the actual observations conform to this assumption. In 4 cases (8 per cent), equal fractions of sodium and chloride were excreted. In only 9 other patients (18 per cent) did the amounts of sodium

and chloride retention correspond within ±5 per cent. Moreover, it appears that patients with relatively little sodium retention may nevertheless retain a great deal of chloride: of 9 patients with 0 to 30 per cent sodium retention, 4 showed a chloride retention of 60 per cent or more. On the other hand, chloride retention seldom keeps pace with an intense sodium retention: of 22 patients with a sodium retention in excess of 60 per cent, only 1 showed a relatively greater chloride retention and 15 showed considerably less chloride retention than expected.

An attempt was also made to correlate the retention of the test dose of water with retention of sodium, chloride or both. However, there were so many uncontrolled variables affecting the urine volume (such as atmospheric temperature and skin evaporation) that the variations were too great to yield statistically significant results in a group of this size.

DISCUSSION

It is a well established observation that blood levels of sodium and chloride often run a parallel course. This observation, and our preoccupation with the study of sodium, potassium and chloride often lead us to ignore the obvious fact that these electrolytes form only a part of, and are dependent upon changes of the total acid-base balance. This fact accounts for the observation of chloride retention without sodium retention and vice versa. It also serves to point out that there is actually no such thing as "sodium chloride" in the electrolyte system and that this term is based on a misconception which antedates our present concepts of acid-base balance.

Tests based on electrolyte balance are commonly used in the diagnosis of pituitary disease, adrenal cortical disease and other conditions. All of these tests rely on chloride changes as the sole criterion or as part of the final equation (*e.g.* the Robinson-Power-Kepler test). One is led to wonder whether or not the substitution of sodium for chloride determinations might not augment their sensitivity.

SUMMARY

The simultaneous urinary excretion of administered sodium and chloride was studied in 50 patients who were referred for endocrine study. Excretion of equivalent amounts of sodium and chloride was found in only 26 per cent. A significant number showed sodium retention without chloride retention and vice versa. It is concluded that these two electrolytes frequently behave in a relatively independent fashion, and that the behavior of one cannot safely be deduced or predicted from investigation of the other element.

REFERENCES

1. ZONDEK, H.: The Diseases of the Endocrine Glands. Berlin, J. Springer, 1926, pp. 197–205.
2. MCQUARRIE, I.; JOHNSON, R. M., and ZIEGLER, M. R.: Plasma electrolyte disturbance in patients with hypercorticoadrenal syndrome contrasted with that found in Addison's disease, *Endocrinology* **21**: 762–772 (Nov.) 1937.
3. WILLSON, D. M.; POWER, M. H., and KEPLER, E. J.: Alkalosis and low plasma potassium in a case of Cushing's syndrome: a metabolic study, *J. Clin. Investigation* **19**: 701–707, 1940.
4. FARNSWORTH, E. B.: Electrolyte partition in patients with edema of various origins: sodium and chloride, *Am. J. Med.* **4**: 338–342 (March) 1948.
5. SUNDERMAN, F. W., and ROSE, E.: Studies in serum electrolytes. XVI. Changes in the serum and body fluids in anorexia nervosa, *J. Clin. Endocrinol.* **8**: 209–220 (March) 1948.
6. GOLDZIEHER, J. W., and STONE, GILBERT C. H.: A rapid colorimetric method for the determination of sodium in biological fluids, *J. Clin. Endocrinol.* **9**: 95–100 (Jan.) 1949.
7. SCHALES, O., and SCHALES, S. S.: Simple and accurate method for determination of chloride in biological fluids, *J. Biol. Chem.* **140**: 879–884, 1941.
8. ASPER, S. P.; SCHALES, O., and SCHALES, S. S.: Importance of controlling pH in the Schales and Schales method of chloride determination, *J. Biol. Chem.* **168**: 779–780, 1947.

THE EFFECT OF TESTOSTERONE PROPIONATE IN A CASE OF PITUITARY TUMOR OBSERVED FOR NINE YEARS*

CHARLES POSNER, M.D.

From the Endocrine Clinic of the Pasadena Dispensary, Out-Patient Department of the Huntington Memorial Hospital, Pasadena, California

IT HAS been demonstrated that pituitary tumors, particularly chromophobe adenomas, can be produced experimentally in animals by prolonged administration of estrogens. This was shown by Cramer and Horning (1), Zondek (2, 3), and Wolfe and Wright (4). Experimental evidence has also been presented by Wolfe and Hamilton (5, 6) that androgens have an inhibitory effect on estrogens in pituitary physiology. However, the value of androgens in ameliorating the symptoms of intracranial pressure caused by a chromophobe adenoma in man has not yet been demonstrated.

The case described here is of interest because of the possible inhibitory effect of testosterone propionate on a pituitary tumor, clinically of the chromophobe type.

CASE REPORT

The patient, W. J., (Fig. 1) a eunuchoid male, 24 years of age, was admitted to the Endocrine Clinic of the Pasadena Dispensary on March 24, 1939. He stated that he had had normal development and hair growth at 15 years of age, having been examined by a school physician at that time. Soon after that he noticed testicular atrophy with gradual disappearance of pubic and axillary hair.

In 1939 he began to experience frontal headaches, which seemed to begin behind the eyes and were worse on the left side. These headaches were of intense, boring, pressing nature. They would last about half an hour and recur three to four times a day. The headaches had been getting progressively worse up to the time of admission. These symptoms were accompanied by a feeling of extreme muscular weakness. The family history was normal except for a thyroidectomy performed on the patient's mother in 1925.

Physical examination

The patient was an apathetic, anemic-looking eunuchoid male, 24 years of age, whose skin had a peculiar, startling pallor. He had a high-pitched boyish voice, and the typical eunuchoid skeletal development and measurements. His height was $70\frac{1}{4}$ inches, his span was $70\frac{1}{4}$ inches, the pubis-to-vertex measurement was $30\frac{3}{4}$ inches, and the pubis-to-floor measurement was 39 inches. His weight was $121\frac{1}{2}$ pounds and blood pressure, 80/60.

There was atrophy of the left optic disc and bilateral temporal hemianopia, more pronounced on the left side. Visual fields were outlined by Dr. Henrietta Johnson on March 27, 1939; they showed marked contraction of the left fields and moderate contraction of the right.

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* A preliminary report on this case was presented before the Los Angeles Society of Neurology and Psychiatry, Feb. 19, 1941.

FIG. 1. A. Patient W. J., age 24, before treatment. B. After fifteen months of treatment with testosterone propionate.

The development of the penis and testes was retarded, with absence of pubic and axillary hair. The testes were both down in the scrotum and were about 1¼ cm. in diameter.

Heart, lungs and abdomen showed no abnormalities.

Laboratory findings

On April 4, 1939, the concentration of serum calcium was 10.2 mg. per cent; serum phosphorus, 3.8 mg. per cent; and plasma cholesterol, 248 mg. per cent. A sugar tolerance test showed 76 mg. per cent for the fasting blood, and 120 mg., 150 mg. and 118 mg. per cent respectively for the ½ hour, 1 hour and 2 hour blood samples. All urine specimens were free of sugar.

A blood count gave the following results: Hgb. 11.3 Gm. (66.9 per cent Newcomer);

R.B.C. 4,040,000; W.B.C. 12,250; neutrophils 40 per cent; monocytes, 5; lymphocytes, 53; and eosinophiles 2 per cent. The basal metabolic rate was minus 9 per cent.

Roentgenograms (Fig. 2) taken on May 9, 1939 showed that most of the epiphyses

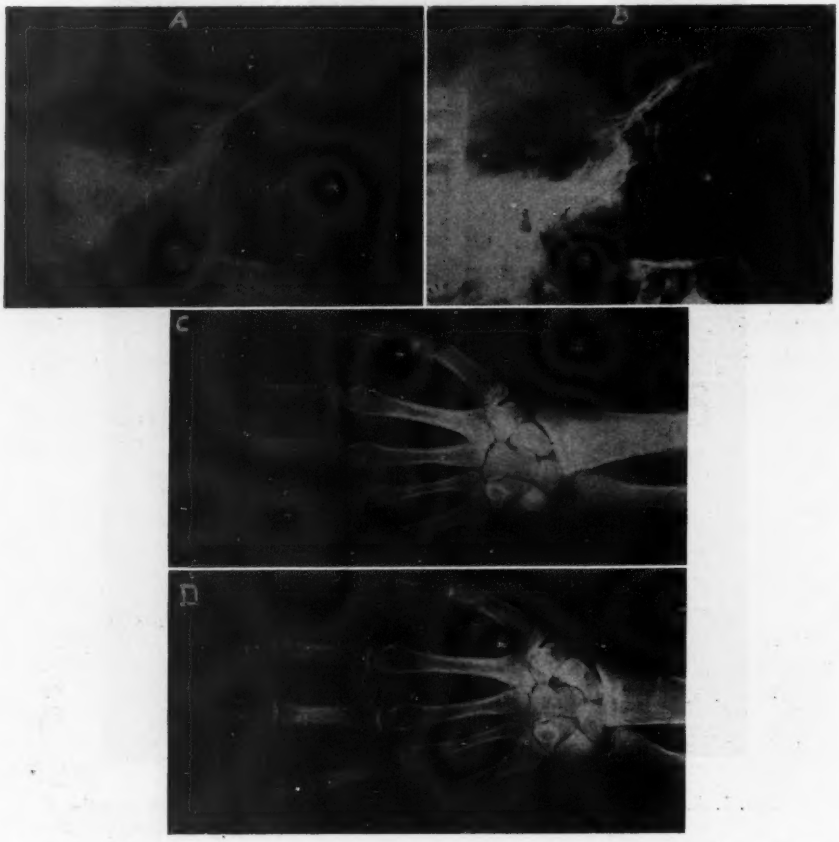

FIG. 2. A. Sella turcica before treatment, showing marked enlargement and erosion of clinoids. B. Sella turcica nine years later. C. Hand, before treatment, showing nonunion of phalangeal and radial epiphyses. D. Complete union of epiphyses nine years after beginning of treatment.

were open, with bone age retardation of 7 years. The sella turcica revealed extensive destruction with displacement of the pineal gland posteriorly. A diagnosis of pituitary tumor was made.

Treatment

At first the patient was treated with 10 mg. of testosterone propionate[1] intramuscu-

[1] I wish to thank Dr. William H. Stoner of the Schering Corporation for supplying the testosterone propionate (Oreton) used in this case.

larly three times a week. From April 14, 1939 to May 24, 1940 the patient received 1090 mg. of testosterone propionate intramuscularly, with resulting increased strength and energy, complete cessation of headaches, moderate growth of pubic and axillary hair with increase in the size of testes and penis. During this interval the patient had obtained a position as a filing clerk, where he had to use his eyes constantly. Visual fields outlined by Dr. Johnson on February 26, 1940 showed considerable improvement in both eyes.

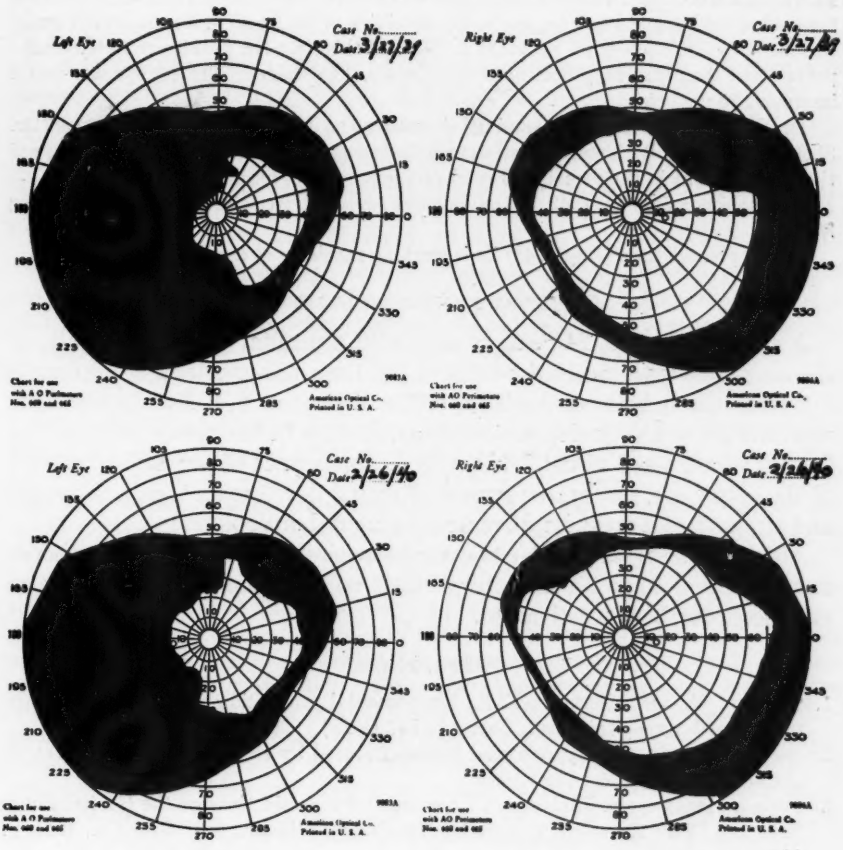

FIG. 3. *Above:* Visual fields before treatment. *Below:* After eleven months of treatment with testosterone propionate.

In the hope of further improvement in the visual fields the patient was given seven x-ray treatments to the pituitary of 150 roentgens each from May 24, 1940 to June 13, 1940 by Dr. John Chapman at the Huntington Memorial Hospital of Pasadena. The following factors were used: 220 K.V., 15 M.A. 2 mm. cu., 1 mm. al filter, 50 cm. distance, 7 circle port, 4 min. 30 sec. for 100 r., 7 min. for 150 r.

Visual fields rechecked by Dr. Johnson on June 10, 1940 revealed further improvement of both fields.

From May 24, 1940 to October 6, 1941 the patient received intramuscularly 2300 mg. of testosterone propionate in oil.

Neurologic examination by Dr. C. Hunter Shelden on December 19, 1940 showed atrophy of the left optic disc. Central field studies using a screen revealed typical evidence of a developing chiasmal lesion. A minimal upper outer quadrant depression was found in the right eye, whereas the field for the left eye showed a complete temporal anopsia as with a central scotoma. The test object used was a white 3 mm. bead. In this examination the field of the left eye was 3 degrees to the nasal side of the fixation. A second field study was made by Dr. Shelden on February 5, 1941. At this time Dr. Shelden reported disappearance of the central scotoma noted previously. The vision in the left eye was found improved 50 per cent.

Dr. Cyril B. Courville also examined the patient on June 13, 1941 and confirmed Dr. Shelden's findings. Both neurologists agreed that surgery should be postponed because of the improvement in the visual fields and disappearance of headaches.

Seen again on July 31, 1942, the patient was energetic, free of headaches and working full time.

At the present time (July 1948) he is working regularly as a public accountant.

SUMMARY AND CONCLUSIONS

A eunuchoid male, 24 years of age, with a pituitary tumor clinically of chromophobe type received a total of 3400 mg. of testosterone propionate intramuscularly between April 14, 1939 and October 6, 1941. The following results were noted during testosterone therapy before x-ray therapy was begun: widening of visual fields with disappearance of headaches, closure of the epiphyses, moderate increase of sexual development, gain in weight and strength and great improvement in mental outlook.

Although the results in this case are promising, the problem of whether or not androgens have an inhibitory effect on chromophobe adenomata in man needs further investigation.

REFERENCES

1. Cramer, W., and Horning, E. S.: Experimental production by estrin of pituitary tumors with hypopituitarism, *Lancet* **1**: 247 (Feb.) 1936.
2. Zondek, Bernhard: Hypophyseal tumors induced by estrogenic hormone, *Am. J. of Cancer* **33**: 555–559 (Aug.) 1938.
3. Zondek, Bernhard: Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation. Baltimore, Williams & Wilkins Co., 1941, p. 119.
4. Wolfe, J. M., and Wright, A. W.: Histologic effects induced in the anterior pituitary of the rat by prolonged injection of estrin with particular reference to the production of pituitary adenomata, *Endocrinology* **23**: 200–210 (Aug.) 1938.
5. Wolfe, J. M., and Hamilton, J. B.: Comparative action of testosterone compounds, of estrone and of combinations of testosterone compounds and estrone on the anterior hypophysis, *Endocrinology* **21**: 603–610 (Sept.) 1937.
6. Wolfe, J. M., and Hamilton, J. B.: Action of testosterone propionate on the structure of the anterior pituitary of the female rat with particular reference to the effects of prolonged administration on the levels of cells, *Endocrinology* **25**: 572–584 (Oct.) 1939.

ABSORPTION AND CLINICAL EFFECT OF A LARGE SINGLE DOSE OF THYROID GLOBULIN

C. L. ROBBINS, M.D.,* AND E. B. MAN, PH.D.

From the Biochemistry Laboratory, Department of Psychiatry, Yale University School of Medicine, New Haven, Conn.

PREVIOUS papers have described a clinical condition similar to hyperthyroidism resulting from continuous ingestion of excessive amounts of desiccated thyroid (1, 2, 3, 4, 5, 6).

In the case to be reported there were no toxic effects, although a serum precipitable iodine of 40.9 gamma per cent established the fact that a great part of a single huge dose of thyroid globulin had been absorbed.

REPORT OF CASE

The patient, M. W., a 31-year-old married white woman, consulted her physician in the latter part of June 1947 regarding her obesity. For two years following her first parturition in 1934, when she was 18 years old, she had weighed 117 pounds. After a right salpingo-oophorectomy and appendectomy at the age of 20, and following a second pregnancy in 1938, her weight was 160 pounds. This increased after her third pregnancy in 1945 to 248 pounds.

The patient's physician prescribed a low calorie diet and 3 grains of thyroid daily. During the first nine days of July 1947 the patient took a total of 27, one-grain, "Proloid" (Maltine) tablets. On the morning of July 10, 1947 the patient took all the tablets remaining in the box, presumably 63 tablets, in a single dose. Promptly repenting, she called a physician, who hospitalized her for observation of the possible evolution of thyrotoxicosis. Twenty-four hours after the ingestion of the drug the basal metabolic rate was plus 4 per cent, at which time the serum contained 40.9 gamma of precipitable iodine and 130.9 gamma filtrate iodine per 100 cc. The serum cholesterol was 116 mg. per cent. Red blood cells numbered 5,100,000 with 13.5 Gm. hemoglobin. White cells were 4,700 with 39 per cent segmented polymorphs, 8 per cent stem cells, 51 per cent lymphocytes and 2 per cent monocytes. The Kahn test was negative. Analysis of a concentrated specimen of urine (sp. gr. 1.030) revealed no abnormalities. The patient was apprehensive on admission when an electrocardiogram was taken, which probably accounts for the tachycardia (110 beats per minute) noted in the tracing. While lying quietly in her hospital bed the pulse rate remained at or about 80 per minute with a maximum of 90. Blood pressure was 130/85 on admission but shortly dropped to levels between 110 and 118 systolic and 68 to 78 diastolic, where it remained during the three days of hospital residence.

Further hospitalization was impossible and likewise bed rest at home was unfeasible so that precise observations of possible changes in circulatory dynamics could not be continued. The patient was able to make frequent visits to the physician's office and on her first visit, two days after discharge from the hospital and the fifth day after the overdose of thyroid, the pulse was 90 per minute, blood pressure 112/76 and the basal metabolic rate minus 3 per cent. Three days later the pulse was 96 per minute, and blood

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* Present address: 4 East Congress, Tucson, Arizona.

pressure 108/78. During this interval the patient continued to feel perfectly well, and her only complaint was failure to lose weight despite strict adherence to a 1000 calorie diet. Her weight at this time was 229 pounds, one pound more than she had weighed on admission to the hospital.

On July 18 an 800 calorie diet was prescribed which the patient faithfully followed with gradual loss of 25 pounds in the ensuing two months. On July 28 the patient experienced transient dizziness when she suddenly rose from a supine position but this experience was not repeated and in general she felt well and happy. The following day the blood serum contained 4.5 gamma per cent precipitable iodine and 6.7 gamma per cent total iodine (total iodine was determined in a separate laboratory). The menstrual period due August 20 was delayed approximately twenty days, an event so unusual that the patient was concerned about possible pregnancy but a *Xenopus laevis* pregnancy test on September 5 gave negative results. When menstruation finally began on September 9 the period was normal in all respects. The next period appeared October 5 and again was "normal" in duration and quantity. Catamenia have been regular since that time. Pulse rates and laboratory findings are recorded in Table 1.

TABLE 1

Date 1947	Pulse	Blood pressure mm. Hg	Weight lbs.	B.M.R. per cent	Serum iodine gamma/100 cc.
July 10	110	130/85	228	—	—
July 11	85	112/72	228	+ 4	Precipitable 40.9 Filtrate 130.9
July 15	86	116/78	228	− 3	—
July 18	96	108/76	229	—	—
July 22	86	—	227	—	—
July 29	88	—	220	−14	Precipitable 4.5 Total 6.7*
Aug. 5	76	112/74	222	—	—
Aug. 12	80	124/84	223	—	—
Aug. 16	80	126/84	219	—	—
Aug. 22	80	118/86	216	−10	—
Sept. 22	76	114/78	205	−15	—
Oct. 31	88	112/86	196	− 9	—

* Total iodine determined in a separate laboratory.

DISCUSSION

The patient ingested 63 grains of "Proloid" containing approximately 8.4 milligrams of organic iodine. Since equi-iodal amounts of thyroid globulin and of racemic thyroxine have been found to be equal in calorigenic potency when tested in myxedematous subjects (7), a dose of 13.3 mg. of thyroxine intravenously would probably be necessary to equal the dose of "Proloid" assuming, of course, that the patient was actually

myxedematous and that absorption from the gut was complete. Complete absorption cannot be proved from the data in this case but the frankly colossal values for total iodine and precipitable iodine in the serum twenty-four hours after ingestion indicate that at least a large part of the thyroid globulin was actually absorbed. Nineteen days later the value for precipitable iodine as well as for total serum iodine had fallen to normal levels.

The fate of the excessive circulating hormone during this interval is not known but from "decay" curves and excretion studies (8, 9) it may be assumed that precipitable iodine concentration diminished rapidly with probable progressive conversion of the protein-bound fraction to the filtrate fraction. It is regrettable that more frequent iodine studies could not have been made.

Of chief interest is the total lack of symptoms and signs of thyrotoxicosis at any time following the absorption of a dose of active thyroid globulin roughly equivalent to a 13.3 mg. dose of racemic thyroxine. Thompson and co-workers (9) gave a single intravenous dose of 10 mg. of thyroxine to a female patient with fully developed myxedema and produced a rise in the basal metabolic rate from minus 45 per cent to minus 6 per cent in seven days with a gradual return to a level of minus 30 per cent over a period of one month. It is reasonable to assume that had the present patient been suffering from true thyroid deficiency of any degree there would have been a detectable response to the huge dose of "Proloid" ingested and absorbed. It is well established that euthyroid individuals have a tolerance for thyroid medication at dosage levels which provoke toxic symptoms in hypothyroid individuals (9, 10, 11). The difference in response to thyroid therapy frequently is the only critical method of differentiating hypometabolism due to thyroid deficiency and hypometabolism due to other causes.

In the present case there is clear evidence of high tolerance and it seems likely that it may be ascribed at least in part to the presence of a normally functioning thyroid gland. Even in a normal euthyroid individual a response to at least the thyroxine fraction of the ingested dose (2.99 mg. of thyroxine in 63 grains "Proloid")[1] could be expected (12). The nature of the conversion of the active hormone to an iodine-containing organic compound present in the blood but incapable of increasing oxidative metabolism of the tissues would be entirely speculative from the data in this case. Recent studies (13) with labelled iodo-casein would suggest that the liver plays an important role in the intermediary metabolism of thyroid hormone.

Two previous rather similar cases, but without determinations of serum precipitable iodine as a measure of circulating hormone have been re-

[1] Based on a letter from Walter Hoskins, Ph.D., Director of Research Laboratories, The Maltine Company, Morris Plains, New Jersey.

ported, in which patients have taken large amounts of thyroid either because of "despondency" or a desire to commit suicide. Goldfinger reported the death of a woman who had taken as much as 100 grains daily (5). Thompson (4) described at length the intake of 80 to 120 grains daily by a physician who subsequent to this self medication developed symptoms of hyperthyroidism and of "psychosis." These cases are cited to emphasize that, although the patient described in this report exhibited no serious symptoms after one massive dose of thyroglobulin, the dangers of self medication with desiccated thyroid can not be ignored. This is only one reason why the present day practice of prescribing desiccated thyroid should be restricted for use by suitable patients.

CONCLUSIONS

A case is reported of a patient who, after ingestion of 63 one-grain tablets of "Proloid" (Maltine), did not develop thyrotoxic symptoms, in spite of a protein-bound iodine of 40.9 gamma per 100 cc. of serum.

From the literature are cited two cases in which continuous ingestion of desiccated thyroid in massive amounts produced thyrotoxic symptoms.

REFERENCES

1. Jahr, H. M.: Thyroid "poisoning" in children, *Nebraska M. J.* **21**: 388 (Oct.) 1938.
2. Riggs, D. S.; Man, E. B., and Winkler, A. W.: Serum iodine of euthyroid subjects treated with desiccated thyroid, *J. Clin. Investigation* **24**: 722–731 (Sept.) 1945.
3. Cohen, L. H., and Fierman, J. H.: Metabolic, cardiovascular, and biochemical changes associated with experimentally induced hyperthyroidism in schizophrenia, *Endocrinology* **22**: 548–558 (May) 1938.
4. Thompson, G. N.: Self induced psychosis with hyperthyroidism complicating manic depressive psychosis: experimental human hyperthyroidism, *Am. J. Psychiat.* **102**: 395–398 (Nov.) 1945.
5. Goldfinger, D.: Excessive self-administered dosages of thyroid extract, *Ann. Int. Med.* **24**: 701–704 (April) 1946.
6. Farquharson, R. F., and Squires, A. H.: Inhibition of the secretion of the thyroid gland by continued ingestion of thyroid substance, *Tr. A. Am. Physicians* **56**: 87–97 1941.
7. Salter, W. T.: The Endocrine Function of Iodine. Cambridge, Mass., Harvard University Press, 1940, p. 111.
8. Schittenhelm, A., and Eisler, B.: Über die Jodausscheidung beim myxödematösen Menschen nach fortgesetzter Thyroxinzufuhr, *Ztschr, f. d. ges. exper. Med.* **86**: 299–308, 1933.
9. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: The calorigenetic action of thyroxin at different levels of basal metabolism in myxedema, *J. Clin. Investigation* **7**: 437–463 (Aug.) 1929.
10. Means, J. H., and Lerman, J.: Symptomatology of myxedema. Its relation to metabolic levels, time intervals and rations of thyroid, *Arch. Int. Med.* **55**: 1–6 (Jan.) 1935.

11. WINKLER, A. W.; LAVIETES, P. H.; ROBBINS, C. L., and MAN, E. B.: Tolerance to oral thyroid and reaction to intravenous thyroxine in subjects without myxedema, *J. Clin. Investigation* **22**: 535–544 (July) 1943.
12. LERMAN, J., and SALTER, W. T.: The calorigenic activity of thyroid iodine at different levels of metabolism, *J. Clin. Investigation* **16**: 678 (Soc. Proc.) (July) 1937.
13. HAMILTON, C. F.; ALBERT, A.; POWER, M. H.; HAINES, S. F., and KEATING, F. R., JR.: The action of iodocasein on human myxedema, with comparative studies on the fate and distribution of synthetic radioactive iodocasein and of I^{131} during hypothyroidism and euthyroidism, *J. Clin. Investigation* **27**: 539 (Soc. Proc.) (July) 1948.

Letters to the Editor

TO THE EDITOR:

THE BUCCAL ADMINISTRATION OF ESTRADIOL

HAVING previously reported that the buccal administration of estradiol in a propylene glycol-alcohol solution affords effective absorption and utilization in a manner comparable with the same quantity of hormone by intramuscular injection (1), the present report deals with the administration of estradiol in solid polyethylene glycol tablets[1] placed within the mouth and absorbed through the buccal mucosa.

Method

The tablets are composed of a polyethylene glycol wax, in which the steroid hormone is soluble, and which is miscible with the oral fluids. They contain 0.1 or 0.25 mg. of pure alpha-estradiol, the primary estrogen of the natural steroid hormone series. A tablet is placed in the mouth in the space between the cheek and the gum of the lower molar teeth, where it gradually dissolves. Insertion of the tablet just before going to sleep at night provides more uniform absorption than when used during the daytime.

Vaginal smears were appraised in all patients at weekly intervals, according to our method previously described, *viz.*, the vaginal material is collected from the lateral wall of the vagina with a dull, curved spatula; it is spread thinly on a clean glass slide and dried with compressed air. The smear is then stained for 20 seconds with 2 per cent aqueous solution of basic fuchsin. Excess solution is washed off with water, the slide is dried with compressed air and is ready for evaluation. This rapid method enables us to determine advisable dosage without delay and is completely adequate for clinical purposes, as proved by twelve years of experience with over 60,000 slides.

Results

In order to determine the effects of this method of administration in cases of estrogen deficiency, 5000 buccal tablets of estradiol were administered to 103 patients during 280 monthly periods. The patients included those with 1) natural or artificial menopause, 2) pituitary-ovarian deficiency and 3) temporary hypo-estrogenism. No patient was treated with "buccal" estradiol unless the clinical response had first been determined to intramuscular alpha-estradiol benzoate or to oral ethinyl estradiol. All but 4 patients showed adequate symptomatic and vaginal cornification response. These 4 were coincidentally disturbed by emotional stress or infection.

Buccal versus intramuscular alpha-estradiol. Menopausal patients who had been given 1.66 mg. of alpha-estradiol benzoate at weekly intervals soon showed typical responses in the vaginal epithelium and subjective

[1] Materials used in this study were supplied by the Schering Corporation.

improvement of the symptoms of estrogen deficiency. This medication was then stopped and the vaginal condition and symptoms of the menopause recurred. The patients then received the estradiol tablets by the buccal route. A daily tablet of 0.25 mg. of estradiol (1.75 mg. per week) was given during the following month. A more complete vaginal cornification and a more pronounced improvement of the subjective symptoms was noted than with the injection method. When 1 mg. of alpha-estradiol benzoate was administered intramuscularly twice a week for one month and was followed by 0.25 mg. of estradiol in buccal tablets daily for one month, it was again found that the clinical and subjective effects of the latter (1.75 mg. per week) exceeded those of the injected hormone (2.0 mg. per week) in most instances; and in all cases were at least equal.

Buccal alpha-estradiol versus oral ethinyl estradiol: Comparisons were made on the basis of 0.1 mg. of buccal estradiol versus 0.05 mg. of oral ethinyl estradiol. The vaginal epithelium responses after the buccal tablets were always as good as, and in the greater number of cases, better than, those with oral ethinyl estradiol. The subjective improvement was invariably more pronounced with the buccal material.

All of the estrogens mentioned here were used so that a fair comparison could be made. None of them gave as complete relief subjectively and objectively as was experienced with the new tablet preparation.

All patients using the buccal tablets experienced an increased feeling of well being. All subjective symptoms due to estrogen deficiency were controlled, and many patients volunteered the information that they had not felt so well in a long time, even when receiving intramuscular injections regularly. No untoward effect of any kind was reported. In menopausal patients symptoms were well controlled; and in those with other ovarian disorders menstrual function was improved. Nervous symptoms were controlled or improved to the point of complete comfort. Vulvar and anal dermatitis (3 patients) disappeared when the vaginal epithelium attained the condition seen in full estrus. Objectively, there was uniform improvement in the vaginal smear, comparable to the subjective improvement. As judged by the smears, all patients showed adequate estrogenic response and a few showed some degree of hyperestrogenic activity, indicating the need for reduced dosage.

Because of the efficiency of the buccal tablets it became increasingly apparent that estrogen should not be administered for more than three of each four weeks, a plan followed here for many years.

While sublingual administration of estradiol in solution in propylene glycol and alcohol affords clinical activity of the same order as that obtained on injection of its esters, the method requires too frequent daily doses and too much dependence on careful cooperation by the patient.

Buccal administration, using the tablet as described, is accordingly less variable in effect. By either method the steroid hormone is absorbed into the systemic rather than into the portal circulation. Physiologically, the buccal route is superior, compared on the basis of the effects of equal doses.

Summary

Alpha-estradiol administered by the buccal route in polyethylene glycol tablets exhibits a high order of clinical efficiency, generally exceeding that of estradiol esters given by injection. This has been demonstrated by the results in 103 patients with estrogen deficiency, in most of whom a daily dose of 0.25 mg. was adequate for control. By this route, as by all other routes used, estradiol is devoid of clinical toxicity.

626 Medico-Dental Building,
Sacramento, California.

GEORGE JOYCE HALL, M.D.
September 30, 1948.

REFERENCE

1. HALL, G. J.: Clinical experiences with the sublingual administration of alpha estradiol, *J. Clin. Endocrinol.* **2**: 26–28 (Jan.) 1942.

TO THE EDITOR:

ANTIHORMONE FORMATION DURING CHORIONIC GONADOTROPIN THERAPY

THE administration of gonadotropic extracts from heterologous sources frequently elicits antihormone formation in man (1) whereas homologous source material does not cause hormone antagonists to develop (2). There are patients whose sera were found to contain substances capable of inhibiting the action of chorionic gonadotropin but in all of these a pituitary extract had also been given (3, 4).

In order to assess possible antihormone formation in response to a highly purified chorionic gonadotropin,[1] serum samples were obtained from patients receiving chorionic gonadotropin for a study of this hormone's effect on the functional life of the corpus luteum (5). One patient received 20,000 I.U. daily from February 12 to March 10 and 10,000 I.U. daily from July 13 to August 3, a total of 760,000 I.U. in two periods of intensive treatment. The patient's serum was tested eleven and thirty-one days after the last injection. The two to three-fold increase in mouse ovarian weight induced by 20 I.U. of chorionic gonadotropin was completely prevented by concomitant administration of the patient's serum. No such antagonistic action, however, could be demonstrated six months after the last injection.

[1] Chorionic gonadotropin (Antuitrin-S) was generously supplied by Dr. D. A. McGinty of Parke-Davis and Company.

Thus, in the absence of any other hormone treatment, a highly purified chorionic gonadotropin excited antihormone formation. It is suggested that the manipulation necessary to gain purity may have altered or denatured the hormone so that it could be antigenic in the large amount administered.

Rutgers University,
New Brunswick, N. J.
and
State University of Iowa,
Iowa City, Iowa.

JAMES H. LEATHEM, PH.D.
JAMES T. BRADBURY, PH.D.
January 19, 1949.

REFERENCES

1. LEATHEM, J. H.: The antihormone problem in clinical endocrine therapy, *J. Clin. Endocrinol.* **4**: 500–504 (Oct.) 1944.
2. LEATHEM, J. H., and RAKOFF, A. E.: Are antihormones formed during pregnancy? *Am. J. Obst. & Gynec.* **51**: 97–99 (Jan.) 1946.
3. SEGALOFF, A., and PARSON, W.: Hypogonadotropic eunuchoidism: report of case with failure to respond to chorionic gonadotropic hormone due to antihormones, *J. Clin. Endocrinol.* **7**: 130–133 (Feb.) 1947.
4. LEATHEM, J. H., and RAKOFF, A. E.: Studies on antihormone specificity with particular reference to gonadotropic therapy in the female, *J. Clin. Endocrinol.* **8**: 262–268 (March) 1948.
5. BROWN, W. E., and BRADBURY, J. T.: A study of the physiologic action of human chorionic hormone, *Am. J. Obst. & Gynec.* **53**: 749–757 (May) 1947.

TO THE EDITOR:

INSULIN THERAPY FOR RELIEF OF PAIN IN OSTEITIS DEFORMANS

SEVERAL years ago I suggested the use of insulin in the treatment of osteitis deformans (Paget's disease). Since then I have continued to use it in many patients in a daily dose of from ten to fifteen units of protamine zinc insulin. The rationale of this therapy is as follows:

It has been found that the majority of patients with osteitis deformans have a lowered sugar tolerance. About one-third of 41 patients with osteitis deformans gave a family history of diabetes. The serum phosphatase level is elevated in the disease and this enzyme is concerned with both bone formation and carbohydrate metabolism.

Insulin is not suggested as a cure or as a remedy to arrest the process, but for the alleviation of pain.

I should like to suggest that other clinicians attempt to verify this in their own cases of osteitis deformans.

964 Fisher Building,
Detroit 2, Michigan.

ROBERT C. MOEHLIG, M.D.
January 24, 1949.

The 1949 Meeting of the Association for the Study of Internal Secretions

FRIDAY AND SATURDAY, JUNE 3 AND 4

Headquarters: Chalfonte-Haddon Hall, Atlantic City, New Jersey.

Registration: Everyone attending the meetings is requested to register. A fee of $1.00 will be charged non-members of the Association. Membership cards should be presented when registering.

The Scientific Sessions: The Scientific sessions will be held in the Viking Room of the Haddon Hall Hotel and programs will begin promptly on schedule. Papers presented at all meetings are planned for ten minutes, unless otherwise noted, and owing to the heavy schedule must be kept within this limit. Manuscripts of all papers should be submitted to the presiding officer or Secretary-Treasurer at the end of the presentation.

Annual Dinner: The Annual Dinner of the Association will be held on Friday evening, June 3, at 7:30 o'clock in the Rutland Room of the Haddon Hall, preceded by cocktails at 6:30 o'clock in the West Room. Secure tickets at time of registration.

Council Meetings: There will be a meeting of the Council on Thursday afternoon, June 2, at 2:00 o'clock, and a luncheon meeting on Friday, June 3.

Business Meeting: The Annual Business Meeting of the Association and Election of Officers will be held at 4:30 p.m., June 4, in the Viking Room of the Haddon Hall.

Local Arrangements: Dr. Matthew Molitch, 705 Pacific Avenue, Atlantic City, New Jersey, is in charge of the local arrangements for the meetings.

Secretary-Treasurer: Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma.

PROGRAM

FRIDAY, JUNE 3, 1949

9:15 a.m.—C. N. H. Long, presiding

1. Piperido-methyl-benzodioxane (933-F): Some Pharmacological and Experimental Observations. By Evan Calkins (by invitation), George W. Dana (by invitation), J. C. Seed (by invitation) and John Eager Howard.

2. Nor-Epinephrine in Adrenal Medulla. By Marcel Goldenberg and Mogens Faber (introduced by R. F. Loeb).

3. Studies on an Anti-Diuretic, Non Chloruretic Substance Extracted from Urines of Normal and Cirrhotic Subjects. By Elaine P. Ralli, Stephen Leslie (by invitation), George H. Stueck, Jr. (by invitation) Mary E. Dumm and Bertram Laken (by invitation).

4. A Method for the Assay of Prolactin in Human Urine. By Richard L. Coppedge (by invitation) and Albert Segaloff.

5. Thyrotrophic and Thyroid Hormone Assay of Normal and Pathologic Human Sera in the Stasis Tadpole. By S. A. D'Angelo, A. S. Gordon, K. E. Paschkis and A. Cantarow.

6. Estimation of Urinary Gonadotrophin of the Non-pregnant Human by the Mouse Uterine Weight and Ovarian Hyperemia Responses. By Charles W. Lloyd, Muriel Morley (by invitation), Kathryn Morrow (by invitation), Julia Lobotsky (by invitation) and Edward C. Hughes (by invitation).

7. Further Studies of Antigonadotrophin Formation in Man. By James H. Leathem and A. E. Rakoff.

8. The Evaluation of the Use of Anterior Pituitary Extract in the Treatment of Pituitary Dwarfism. By Joseph C. Edwards, Cecil M. Charles (by invitation) and Cyril M. MacBryde.

9. On the Inability of Adrenocorticotrophic Hormone or Epinephrine to Deplete the Ascorbic Acid of the Chick Adrenal. By Norman F. Boas (by invitation) and Joseph W. Jailer.

10. Regulation of Pituitary Adrenocorticotrophic Activity by Adrenal Cortical Hormones. By Chi-Ping Cheng (introduced by George Sayers).

11. Adequacy of Pituitary Adrenocorticotrophic Function in Nutritional Deficiencies. By George Sayers.

12. Effects of Prolonged Adrenal Cortical Stimulation upon Free and Esterified Serum Cholesterol in Normal Men. By Jerome W. Conn, and William C. Vogel (by invitation).

13. Possible Involvement of the Adrenal Cortex and Thyroid in Mobilization of Fat to the Liver. By Louis Levin.

FRIDAY, JUNE 3, 1949

2:00 p.m.—J. S. L. Browne, presiding

14. Stimulation of Nitrogen by Adrenal Cortical Extract during Insulin Hypoglycemia. By Frank L. Engel.

15. Renal Function in Normal and Adrenalectomized Rats following Saline or Adrenal Steroid Administration. By W. R. Boss (by invitation) James H. Birine and Robert Gaunt.

16. Adrenal Cortical Hormone in Blood. By K. E. Paschkis, A. Cantarow and D. Boyle (by invitation).

17. Urinary Corticoids. By Eleanor H. Venning, M. P. Ripstein (by invitation) and V. E. Kazmin (by invitation).

18. Studies on the Interrelationship of Adrenal and Thyroid Function. By Robert S. Reiss, Peter H. Forsham (by invitation) and George W. Thorn.

19. Clinical and Metabolic Changes in Addison's Disease Following the Administration of Compound E Acetate (11-dehydro, 17-hydroxy-corticosterone acetate). By P. H. Forsham (by invitation), L. L. Bennett (by invitation), M. Roche (by invitation), R. S. Reiss, A. Slessor (by invitation), E. B. Flink (by invitation) and G. W. Thorn.

20. Effect of a Single Dose of Desoxycorticosterone Acetate on Electrolyte Metabo-

lism. By Paul Fourman (by invitation), Edwin J. Kepler, Edward C. Reifenstein, Jr., and Eleanor F. Dempsey (by invitation).

21. Changes in Urinary Steroids Produced by Sodium Deprivation and by Desoxycorticosterone Acetate Administration. By William H. Daughaday (by invitation) and Cyril M. MacBryde.

22. The Evaluation of Adrenocortical Function by Ascertaining the Reponse to a Single Injection of Adrenocorticotrophin. By H. W. McIntosh (by invitation), B. Singer (by invitation) and M. M. Hoffman.

23. The Level of Circulating Eosinophils as an Indicator of Adrenal Cortical Adequacy Following Major Surgery. By Marcel Roche (by invitation), A. Gorman Hills (by invitation) and George W. Thorn.

24. Is the Protein Metabolic Abnormality of Cushing's Syndrome Catabolic or Anti-Anabolic? By Sheldon Margen (by invitation), Laurence W. Kinsell, Erin K. Flanagan (by invitation), Lila E. Suiter (by invitation) and Elliot Rapaport (by invitation).

25. Hypokaliemic Alkalosis in Cushing's Syndrome. Observations on the Effects of Potassium Chloride and Testosterone Proprionate Therapy. By Robert Teabeaut (by invitation), Frank L. Engel, and Haywood M. Taylor (by invitation).

26. The Mechanism of Action of Testosterone in the Therapy of Cushing's Syndrome. By Frederick C. Bartter (by invitation), Anne P. Forbes, William M. Jefferies, Evelyn L. Carroll (by invitation), and Fuller Albright.

SATURDAY, JUNE 4, 1949

9:00 a.m.—E. A. Doisy, presiding

27. Metabolism and Distribution of Thiourea in the Rat as measured with Radioactive Sulfur. By John Schulman, Jr. and Richard P. Keating (introduced by Rulon W. Rawson).

28. The Tracer Technique with Radioiodine I^{131} as a Potential Substitute for the Basal Metabolic Rate Determination in Routine Clinical Practice. By Sidney C. Werner.

29. The Distribution and Metabolism of Circulating Testosterone. By C. D. West and L. T. Samuels.

30. Pseudo-hypoparathyroidism: A Report of Two New Cases witb Special Reference to the Epiphyseal Changes. By Harold Elrick (by invitation), Frederic C. Bartter (by invitation), Adney Sutphin (by invitation) and Fuller Albright.

31. Quantitative Measurements of the Growth of Axillary Hair as an Index of the Endocrine Status. By James B. Hamilton.

32. The Effects of Testosterone Propionate on the Peripheral Blood and Bone Marrow of Women with Advanced Carcinoma of the Breast. By Timothy R. Talbot, Jr. (by invitation) and George C. Escher.

33. Effects of Small Doses of Testosterone Propionate on Spermatogenesis. By Cleve Beller (by invitation) and Henry H. Turner.

34. Endocrine Factors in Gout: The Significance of Differences in Childhood and Adult Urate Metabolism. By William Q. Wolfson, David Krevsky, Rachmiel Levine (by invitation), Kinu Kadota (by invitation) and Clarence Cohn.

35. The Effect of Castration, of Unilateral Castration and of Pregnancy in Unilaterally Castrate Rats on the Ovary Transplanted into the Spleen. By Gerson R. Biskind and Morton S. Biskind.

36. The Occurrence of Conjugated Sulfates of Estrogens in Human Pregnancy Urine. By Herman Cohen (by invitation) and Robert W. Bates.

37. Hormonal Factors Producing the Gametokinetic Response in the Male Frog (Rana Pipiens). By Robert B. Greenblatt, Sarah Clark (by invitation) and R. M. West (by invitation).

38. Action of Estrogens on Release of Luteinizing Hormone in Menopausal Women. By Arthur A. Hellbaum, J. W. Funnell (by invitation) and E. C. Keaty (by invitation).

39. The Hormonal Pattern in Pseudocyesis. By A. E. Rakoff and Paul H. Fried (by invitation).

40. Management of Threatened Abortion in the Human with Large Doses of Prethylstilbestrol. By A. B. Abarbanel.

SATURDAY, JUNE 4, 1949

2:00 p.m.—C. H. Best, presiding

41. A Hyperglycemic Factor Extracted from the Pancreas. 10 mins. By I. J. Pincus (introduced by A. E. Rakoff).

42. Studies in Carbohydrate Metabolism in Decerebrate Rats. 10 mins. By Evelyn Anderson and Webb Haymaker (by invitation).

43. Factors Affecting the Volume of the Islands of Langerhans. 15 mins. By R. E. Haist, Margaret Evans and B. Kinash (introduced by C. H. Best).

44. Studies on the Serum Potassium in Diabetic Acidosis. 15 mins. By Carl S. Nadler, Samuel Bellett and Mary Lanning (introduced by C. H. Best).

45. Pyruvic and Citric Acid Metabolism. 15 mins. By Max Miller and Ernest Bueding (introduced by C. H. Best).

46. Changes in Inorganic Serum Phosphorus during the Intravenous Glucose Tolerance Test as an Adjunct to the Diagnosis of Early Diabetes Mellitus. 15 mins. By Peter H. Forsham (by invitation), Marcel Roche (by invitation) and G. W. Thorn.

47. The Metabolism of Glucose and Galactose when Administered Simultaneously to Man. 10 mins. By G. C. Walsh (by invitation), M. M. Hoffman, H. T. McAlpine (by invitation) and E. H. Mason (by invitation).

48. Studies in Fat Metabolism. 1. Steroid Hormonal Effects Upon Blood Ketones and Other Intermediate Products of Fat and Protein Catabolism. 10 mins. By Laurance W. Kinsell, Sheldon Margen (by invitation), George D. Michaels (by invitation), Betty T. Signorotti (by invitation) and David P. McCallie (by invitation).

49. The Urinary Excretion of Corticosteroids in Diabetic Acidosis. 10 mins. By Janet W. McArthur, Randall G. Sprague and Harold L. Mason.

50. Steroid Diabetes Associated with Cushing's Syndrome and Excretion of 17-Hydroxycorticosterone (Compound F) in Urine; Metabolic Studies. 10 mins. By Randall G. Sprague, Alvin B. Hayles (by invitation), Harold L. Mason, Marschelle H. Power (by invitation) and Warren A. Bennett (by invitation).

51. Behavior of Electrolytes During Treatment of Diabetic Keto-Acidosis. 10 mins. By Jonas Weissberg, (by invitation), Thomas H. McGavack, A. M. Shearman (by invitation) and I. J. Drekter.

TO BE READ BY TITLE

52. Correlation of Vaginal Smears and Endometrial Biopsies in Normal Cycles and in Gynecic Disorders. By H. E. Nieburgs, Robert B. Greenblatt and S. Bamford (by invitation).

53. The Effect of Pteroylglutamic Acid Antagonists on the Response of the Reproductive Accessories of C57 Male Mice to Testosterone. By E. D. Goldsmith, H. M. Black (by invitation) and R. F. Nigrelli (by invitation).

54. Synthesis of Testosterone from Androstenedione-3, 17 by Testis Tissue. By Leo T. Samuels, Blaine H. Levedahl (by invitation), M. L. Helmreich (by invitation), and M. M. Pottner (by invitation).

55. The Role of the Adrenal Cortex in Some Somato-Sexual Aberrations in Infants and Children. By M. M. Melicow.

56. Effects of Compound E on Blood Ketone Bodies. By Leslie L. Bennett (by invitation), Alexander Slessor (by invitation) and George W. Thorn.

57. The Effect of Dietary Protein on the Ability of the Liver to Inactivate Estradiol in the Rat. By Joseph W. Jailer.

58. Pregnanediol Excretion in Cases of Blighted Ovum. By A. B. Abarbanel, Robert Hoyt (by invitation) and M. G. Levine (by invitation).

59. A Mechanism of Potassium Deficiency in Alkalosis. By Charles H. Burnett, Belton A. Burrows (by invitation) and Robert R. Commons (by invitation).

60. Effects of Hemopoietic Agents on Blood Formation in Hypophysectomized Rats. By Robert Gerstner (by invitation) and Albert S. Gordon.

61. The Relative Effectiveness of Desoxycorticosterone Acetate in Oil Solution and in Pellets Diluted with Cholesterol. By Albert Segaloff.

62. Adrenal Cortex Activity in Essential Hypertension. By Louis Tobian, Jr. and Harold Joseph (introduced by Carl A. Bunde).

63. The White Blood Cell Response of Rats to Adrenalectomy, Stress, and Pantothenic Acid. By Mary E. Dumm, Paul Roth (by invitation), Paul Ovando (by invitation) and Elaine P. Ralli.

64. Role of Emotional Stress in the Survival of Adrenalectomized Rats given Replacement Therapy. By Miguel R. Covian (introduced by Curt Richter).

65. The Androgenic Activity of New Esters of Testosterone. By A. J. Bergmann and Lloyd C. Miller (introduced by John S. L. Browne).

66. Effect of Androgen and Growth Hormone on the Rat's Os Penis. By Wm. R. Lyons, Edward Abernethy (by invitation) and Mark Grooper (by invitation).

67. The "Thiocyanate Space" and "Iodide Space" in the Thyroid Gland. By J. F. McClendon, William C. Foster (by invitation) and Emerson Reed (by invitation).

68. A Comparison of the 17-Ketosteroid Excretion of Cases of Cushing's Syndrome Due to Adrenal Tumor with Those Due to Hyperplasia (Hyperfunction). By Anne P. Forbes, Evelyn L. Carroll (by invitation) and Mary L. Wheeler (by invitation).

69. Sex Hormones and Staphylococcus Infections. By Manuel Villaverde.

70. The Problem of Allergy to Steroid Hormones. By George P. Heckel.

71. Intravenous Estrogen in Menometrorrhagia in the Human. By A. R. Abarbanel.

72. The Incidence of Cancer in Endocrine Case Histories. By J. K. Fancher and Jean Brooks (by invitation).

73. Renal Clearances in Patients with Cirrhosis of the Liver, with and without Ascites By Stephen H. Leslie, Barbara Johnson (by invitation) and Elaine P. Ralli.

74. Porphyria Simulating Anorexia Nervosa. By Bernard A. Watson.

75. Hemosedimentation Test in Obesity. Aulo Pinto Viégas.

76. The Effects of Vitamin B, Thyroid, and Adrenal Alterations on the Amino Acid Oxidase Activity of Rat Liver and Kidney. By Samuel R. Tipton and Frances M. Colvin (by invitation).

77. The Problem of Endemic Goiter in Yunnan Province. By Isidor Greenwald.

The 1949 Meeting of the American Goiter Association

The annual meeting of the American Goiter Association will be held at the Loraine Hotel in Madison, Wisconsin, May 26 to 28, 1949. All members who have not made their hotel reservations are urged to do so immediately.

PROGRAM

Dietary Factors in the Pathogenesis of Simple Goiter.
Monte A. Greer, M.D., Martin G. Ettlinger, M.D., and E. B. Astwood, M.D., Boston, Massachusetts

Comparative Activity of Thiouracil and Other Antithyroid Compounds in the Rhesus Monkey.
D. A. McGinty, M.D., and M. L. Wilson, M.D., Detroit, Michigan

The Metabolic Fate of the Thyroid Hormone or its Derivatives.
W. T. Salter, M.D., New Haven, Connecticut

Metabolic Studies with I^{131} Labelled Thyroid Compounds.
Alexander Albert, M.D., and F. Raymond Keating, M.D., Rochester, Minnesota

The Calorigenic Properties of Tetrabromthyronine Tetrachlorthyronine as Assayed in Human Myxedema.
Jacob Lerman, M.D., Boston, Massachusetts

Thyroid Hormone-Like Properties of Tetrabromthyronine and Tetrachlorthyronine.
Charles E. Richards, M.D., Roscoe O. Brady, M.D. and Douglas S. Riggs, M.D., Boston, Massachusetts

The Antithyroxin Activity of Thyroxin Analogues.
Ruth Cortell, M.D., New York, New York

Thyroid-thyrotrophic Hormone Interaction in Body Fluids as Tested in the Starved Tadpole.
Savino A. D'Angelo, M.D., New York, New York

The Van Meter Prize Award Paper.
To be presented by winner of the Award

The Confessions of an Elderly Thyroidologist.
J. H. Means, M.D., Boston, Massachusetts

The Effects of Massive Doses of Potassium Iodide.
T. S. Danowski, M.D., Pittsburgh, Pennsylvania

The Thyroxin-like Action of Elemental Iodine
Samuel Dvoskin, M.D., New York, New York

The Functional Capacity of Various Types of Thyroid Carcinoma as Revealed by the Autoradiographic Demonstration of Radioactive Iodine.
Patrick J. Fitzgerald, M.D., New York, New York

A Method for the Preoperative Estimation of Function of Thyroid Tumors: Its Significance in Diagnosis and Treatment.
Brown M. Dobyns, M.D., and Bengt N. Skanse, M.D., Boston, Massachusetts

Thyroidectomy. (Round Table Discussion)
Richard B. Cattell, M.D., Boston, Massachusetts

Antithyroid Drugs. (Round Table Discussion)
E. B. Astwood, M.D., Boston, Massachusetts

Radioactive Iodine. (Round Table Discussion)
Mayo Soley, M.D., Iowa City, Iowa

Current Treatment of Hyperthyroidism. (Round Table Discussion)
John de J. Pemberton, M.D., Rochester, Minnesota

Treatment of Hyperthyroidism. (Round Table Discussion)
J. H. Means, M.D., Boston, Massachusetts

When is a Malignant Goiter Malignant?
Robertson Ward, M.D., San Francisco, California

Incidence of Carcinoma of the Thyroid in Nodular Goiter.
Warren Cole, M.D., Chicago, Illinois

What Thyroid Nodules Are to be Feared? A Basis for Deciding upon Surgical Exploration.
Oliver Cope, M.D., Boston, Massachusetts

Papillary Tumors of the Thyroid.
Shields Warren, M.D., Boston, Massachusetts

Non-encapsulated Sclerosing Tumor of the Thyroid.
J. Beach Hazard, M.D., and George Crile, Jr., M.D., Cleveland, Ohio

The Natural History of Thyroid Cancer.
Edgar L. Frazell, M.D., and Frank W. Foote, Jr., M.D., New York, New York

Lymphosarcoma of the Thyroid
Robert S. Dinsmore, M.D., Cleveland, Ohio

Surgical Treatment of Carcinoma of the Thyroid.
B. Marden Black, M.D., Rochester, Minnesota

Radio-Iodine Therapy of Metastatic Carcinoma of the Thyroid: A Six Year Progress Report.
S. M. Seidlin, M.D., Miss E. Oshry, I. Rossman and E. Siegel, New York, New York

Radio-Iodine in the Treatment of Metastic Cancer of the Thyroid—Credits and Debits.
Jack B. Trunnell, M.D., Miss Ruth Hill, Benedict J. Duffy, Jr., M.D., Leonidas Marinelli, M.D., Wendell Peacock and Rulon W. Rawson, New York, New York

Presidential Address—"Henry S. Plummer"
Arnold S. Jackson, M.D., Madison, Wisconsin

The Problem of Cancer of the Thyroid in a Non-Endemic Goiter Area
David H. Poer, M.D., Atlanta, Georgia

Some Goiter Problems Met With at West China Union University, Chengtu, Szechwan, China.
Charles H. Arnold, M.D., Lincoln, Nebraska

Cretinism.
Harry Colfer, M.D., Madison, Wisconsin

New Discoveries on the Innervation of the Larynx.
Brien T. King, M.D., and Ralph Gregg, M.D., Seattle, Washington

Metabolism Testing Under Anesthesia in Normal and Hyperthyroid Subjects.
Elmer C. Bartels, M.D., Boston, Massachusetts

Relationship of Lymphocytes and Fibrous Replacement to the Incidence of Postoperative Myxedema.
F. B. Whitesell, Jr., M.D., and B. Marden Black, M.D., Rochester, Minnesota

Struma Lymphomatosa.
T. C. Davison, M.D., and A. H. Letton, M.D., Atlanta, Georgia

Total Thyroidectomy: A Supplemental Report of 280 Cases of Diffuse Toxic Goiter Treated by this Method.
A. C. Scott, Jr., M.D., and P. M. Ramey, M.D., Temple, Texas
Pneumothorax Following Thyroidectomy (A Report of Two Cases)
Lindon Seed, M.D., Chicago, Illinois
A Simplified Clinical Method for the Determination of Blood Iodine.
Arthur C. Connor, M.D., Roy E. Swenson, M.D., George M. Curtis, M.D., Columbus, Ohio
Treatment of Recurrent Hyperthyroidism.
William S. Reveno, M.D., Detroit, Michigan

The 1949 Annual Meeting of the American Diabetes Association

CHALFONTE-HADDON HALL,
ATLANTIC CITY, N. J.
SATURDAY AFTERNOON, JUNE 4;
SUNDAY MORNING AND AFTERNOON, JUNE 5.
BANQUET, SATURDAY NIGHT.

Please send reservations for the banquet now to this office. Wives of members are welcome. Dinner subscriptions—$6.00—*Payable when you register* at the meeting.

LAURENTIAN HORMONE CONFERENCE

The Laurentian Hormone Conference of the A.A.A.S. will hold its 1949 meeting at the Forest Hills Hotel, Franconia, New Hampshire, September 12 through 17.

Attendance at this Conference is limited by the accommodation available at the hotel but the Committee on Arrangements invites applications for attendance from interested investigators and specialists in the hormone field. The Committee on Arrangements consists of R. W. Bates, E. R. Squibb & Sons; R. D. H. Heard, McGill University; A. D. Odell, Charles E. Frosst & Co.; E. C. Reifenstein, Jr., Sloan-Kettering Institute; A. White, School of Medicine, University of California at Los Angeles; and G. Pincus, Chairman, The Worcester Foundation for Experimental Biology.

Applications for attendance at the Conference should be sent to the Chairman at 222 Maple Avenue, Shrewsbury, Massachusetts. Applications to be considered by the Committee must be received by June 6, 1949.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: ROY HERTZ. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS

PANCREAS

HILES, C.: Gastric secretory response in hypoglycemia as produced during insulin shock therapy, *Am. J. M. Sci.* **214**: 667–672, 1947.

The purpose of this report is to emphasize that insulin shock therapy as employed in the treatment of mental disease may cause serious side effects. The study reveals the increase in gastric acidity in patients with schizophrenia when given insulin shock therapy.

After a limited review of the literature, five cases are reported including graphs on the following data: sugar, total acid, free acid, blood, coma and bile.

The cases illustrate the effect of hypoglycemia upon gastric secretion. In these 5 cases of schizophrenia given insulin shock treatment, a definite increase in the acid content of the stomach occurred during the periods of hypoglycemia and since it is believed that gastric hyperacidity is one of the contributory factors in the production of peptic ulcer, thorough gastro-intestinal studies should be completed in such patients before giving insulin. Measures to counteract or nullify the gastric secretory response to hypoglycemia should also be instituted.—*E.C.R., Jr.*

LEECH, R. S., and FORD, N. W.: A simple bedside method for the estimation of blood sugar, *J. Lab. & Clin. Med.* **33**: 644–650, 1948.

A simple method for rapid estimation of blood sugar, based on the reduction by glucose of dinitrosalicylic acid, was designed primarily for the physician or nurse with a minimum of time and equipment and limited laboratory facilities. In its present form, the method is not suitable for estimating very low blood sugar values; between 50 and 75 mg. per cent it is possible to make fairly good approximations. Comparison of the results obtained on 60 blood samples, using the method described, with those of other standard methods, shows that they check closely with the determinations as carried out by the Folin-Wu macrométhod and the Folin-Malmros or the rapid Hagedorn-Halstrom-Jensen micromethods.—*T.H. McG.*

MILLARD, E. B., and ROOT, H. F.: Degenerative vascular lesions and diabetes mellitus, *Am. J. Digest. Dis.* **15**: 41–51, 1948.

The authors analyzed the autopsies of 110 diabetic patients who had been studied at the New England Deaconess Hospital from 6 months to 29 years and whose deaths occurred between 1940 and 1945. The average duration of life after the onset of diabetes was 9.8 years. The average life expectancy in this group was 44 per cent of the general popula-

tion average. Among the younger patients (less than 33 years of age) who died within six years of the development of diabetes, none showed arteriosclerosis. When diabetes had been present in this group for more than 14 years, all patients showed severe degenerative vascular lesions (coronary atheromata, intercapillary glomerulosclerosis, pyelonephritis, nephrosclerosis and chronic glomerulonephritis), and hypertension. Among the 100 patients analyzed, the cause of death was directly attributable to diabetes in 5 instances; diabetes was a "critical factor" in the deaths of 85 patients. Diabetic coma accounted for 3 per cent of the deaths. Thirty-six per cent of the deaths were due to degenerative heart disease. Sixty-eight per cent of the hearts examined showed some degree of coronary artery narrowing. Forty-one per cent of the patients had no palpable dorsalis pedis artery pulsations before death. Degenerative vascular lesions in the kidneys were seen in 52 per cent of the cases. Abnormalities in the pancreas were noted in 79 per cent of the patients. Hypertension was present in 59 per cent of the people examined.

The authors felt that premature vascular lesions were postponed in those cases in which diabetic coma, acidosis, and hypoglycemic reactions were avoided by careful medical management.—*H.S.G.*

MIRSKY, I. A.; PODORE, C. J.; WACHMAN, J., and BROH-KAHN, R. H.: The urinary excretion of insulin by normal and diabetic subjects, *J. Clin. Investigation* **27**: 515–519, 1948.

The problem of urinary excretion of insulin has been reinvestigated in an effort to clarify previous conflicting reports. A procedure was devised for assaying small quantities of insulin which had been added to urine before and after lyophilization. Results of assays in normal and diabetic subjects showed statistically significant differences; the average daily excretion of insulin by normal subjects was 0.16 ± 0.04 units, that of mildly diabetic subjects who did not require insulin 0.07 ± 0.03 units. Of even greater interest was the finding that both normal and diabetic subjects excreted only infinitesimal fractions of large doses of exogenous insulin. Two diabetic patients with "insulin resistance" excreted less than did nondiabetic subjects who had received large amounts of exogenous insulin. One of these patients, requiring 240 units per day, excreted 0.2 units daily; the other, with a daily requirement of 350 units, excreted 0.3 units. In comparison to these figures, 0.6 units were excreted by the nondiabetic subject after injection of 400 units. The assumption that insulin undergoes a rapid destruction within the body is indicated by the data from these studies.—*T.H.McG.*

MOSENTHAL, H. O.: Management of diabetes mellitus; an analysis of present day methods of treatment, *Ann. Int. Med.* **29**: 79–90, 1948.

This is a review article which proposes a three point plan in the management of diabetes. The value of normal blood sugar concentrations and avoidance of glycosuria is recognized, but the avoidance of hypoglycemia is the paramount consideration. Adjustment of food intake, diet calculations, auto-urine analysis, and medical supervision is fundamental. Attention should be given to the conservation of qualitative nutrition as measured by hemoglobin, red blood cell count, serum protein levels, and avoidance of obesity—*C.D.D.*

PALMER, L. J.; CRAMPTON, J. H., and BARNES, R. H.: Pregnancy in the diabetic, *West. J. Surg.* **56**: 175–177, 1948.

Thirty-nine pregnancies in 37 diabetic women are the subject of this study. Diethyl-

stilbestrol and progesterone were given to the patients in varying amounts. Compared to a group reported previously by the same authors, in which no hormones were employed, the current group exhibited an increase in fetal survival from 60 to 76.9 per cent—*J.M.*

REED, J. A.: Statistical analysis of deaths from diabetes in the District of Columbia for a period of 42 years– –1903–1944 inclusive. Preliminary report and analysis: a comparison of two five-year periods –1903–1907 and 1940–1944, *Am. J. Digest. Dis.* **15**: 233–238, 1948.

The author's analysis was based on data obtained from the death certificates, signed by the attending physician, which were filed with the Division of Vital Statistics of the Health Department of the District of Columbia. The cases were divided into two groups: 1) those in which diabetes was the immediate or primary cause of death, and 2) those in which diabetes was a secondary or contributing cause of death. The two five-year periods represent intervals approximately 20 years before and after the institution of insulin therapy. Although the population of the area increased $2\frac{2}{3}$ times between 1903 and 1944, the deaths due to diabetes increased fivefold. In the 1903–1907 period, 77.5 per cent of the deaths of diabetics were due primarily to diabetes; in the 1940–1944 period, this figure dropped to 27.5 per cent. The author felt that this significant change was due to better medical management of diabetes through diet and insulin. With improved therapy, patients lived longer and other primary causes of death came to the fore. Whereas males constituted 53 per cent of diabetics who died in the first period, they constituted only 37 per cent in the second period. Between 1903 and 1907, 70 per cent of the population was white and 30 per cent was colored: ninety-two per cent of the diabetic dead were white and 8 per cent were colored. Although the population composition between 1940 and 1944 remained the same as in the earlier period, the whites accounted for 71 per cent of the deaths and the colored for 29 per cent of the deaths in the later period. When diabetes was the primary cause of death in those cases complicated by gangrene, the incidence of these cases was 8 per cent in the 1903–1907 period and 19 per cent in the 1940–1944 interval. Similarly where coma and/or acidosis complicated diabetes, the incidence rose from 49 per cent to 55 per cent. However, when these complications were present in the cases which included deaths primarily due to diabetes as well as deaths in which diabetes was a contributing factor, the incidence fell from 40 per cent to 17 per cent. The average age at death of all diabetics in both periods was the same (59.7 years). The average age of those patients in which death was primarily due to diabetes was 50 years in the period 1903–1907 and 54.6 years in the period 1940–1944. It was pointed out that the percentage of cases treated in hospitals rose from 19 per cent to 53 per cent. Where diabetes was a contributing cause of death, the incidence of cardiovascular-renal diseases remained unchanged in the two periods.—*H.S.G.*

SCHWARTZMAN, J.; CRUSIUS, M. E., and BEIRNE, D. P.: Diabetes mellitus in infants under one year of age: report of a case and review of the literature, *Am. J. Dis. Child.* **74**: 587–606 (Nov.) 1947.

This is a general review of the subject wherein 57 cases of diabetes mellitus in infants under one year reported in the literature to date are presented in tabular form (from as early as 1850) giving the author and reference, age at onset, sex, family history of dia-

betes, symptoms, laboratory findings (glycosuria, blood sugar), outcome, and autopsy observations. To these, a case of an 8-month-old girl with diabetes mellitus is added.

Heredity, infections and disorders of the central nervous system were the main etiologic factors, in the order given. Early symptoms may be loss of weight, dry or sensitive skin, irritability and/or crystalline deposits on the diapers. Common complications were observed to be: dermatologic conditions, gangrene, cataract, infections of the respiratory tract, acidosis and coma. The mortality rate of 50 cases was calculated, these having been divided into two periods—the preinsulin period extending to 1924, and the insulin period, from 1925 to the present. The figures were 88.5% and 50% respectively. The commonest observations at autopsy were atrophy of the pancreas, with decrease in size and number of the islands of Langerhans, and fatty degeneration of the liver.

Treatment is based on a diet approaching the normal one, supplemented with insulin and vitamins, as needed. Furthermore, it is evident that the earlier the onset of diabetes mellitus, especially if the patient is under 3 months of age, the worse the prognosis; and the longer the disease has persisted unrecognized and without proper treatment, the poorer the outlook.

It is concluded, that from the standpoint of the formulation of a prophylactic program, early detection of the disease is most important, so that proper care may be instituted. The following procedures are recommended: 1) in all cases with a familial history of diabetes: routine dextrose tolerance tests every two months for the first year and every six months thereafter; 2) during infections: daily urinalysis, with sugar tolerance tests at the onset and at the end of the illness; 3) after any infection: routine urinalysis every two weeks for a period of 3 months, followed by a dextrose tolerance test at the end of that time.—*E.C.R., Jr.*

TUYNMAN, P. E., and WILHELM, S. K.: Potassium deficiency associated with diabetic acidosis, *Ann. Int. Med.* **29**: 356–361, 1948.

A case report is presented of a patient who developed respiratory distress and weakness seven and a half hours after treatment for diabetic acidosis had begun. The respiratory embarrassment was not relieved by oxygen but was rapidly relieved by oral potassium chloride.—*J.M.*

VERZAR, F., and WENNER, V.: The influence *in vitro* of desoxycorticosterone on glycogen formation in muscle, *Biochem. J.* **42**: 35–41, 1948.

Surviving rat diaphragm synthesizes glycogen in Ringer solution containing glucose. This process is accelerated by insulin and inhibited by desoxycorticosterone. The effect of 1 unit of insulin is completely inhibited by 5 to 10 mg. of the latter hormone.—*H.L.M.*

WILKERSON, H. L. C., and HEFTMANN, E.: Screening method for blood glucose, *J. Lab. & Clin. Med.* **33**: 236–238 (Feb.) 1948.

A simple and inexpensive method for blood glucose has been described. It is a modification of Hagedorn's potassium ferrocyanide method. The method, using 0.1 ml. of blood and reagents in tablet form, is so designed as to demonstrate the presence of sugar within 5 minutes, only if the concentration is above an artibrarily selected critical level. In 50 cases examined by this method 25 blood samples below 170 mg. per cent glucose gave a negative result, 21 samples above 180 mg. per cent a positive result and four samples between 170 and 180 mg. per cent either a positive or a negative result.—*T.H.McG.*

ZIMMERMANN, B., and DONOVAN, T. J.: Hyperglycemic effect of insulin, *Am. J. Physiol.* **153**: 197–204, 1948.

Commercial insulin possesses a hyperglycemic property which is not destroyed when the hypoglycemic effect is inactivated. Amorphous and crystalline insulin inactivated with cysteine showed equal hyperglycemic effects in dogs with respect to magnitude and duration. In pancreatectomized dogs not treated with insulin the hyperglycemic response was small and the blood ketone bodies rose simultaneously with the blood sugar following administration of both natural and inactivated insulin. The inactivated insulin does not protect mice against insulin convulsions. It is concluded that the hyperglycemic principle acts on the hepatic glycogen reserves but does not neutralize the hypoglycemic effect of insulin.—*A.E.M.*

GENERAL

DE VRIES, A., and ALEXANDER, B.: Studies on amino acid metabolism. II. Blood glycine and total amino acids in various pathological conditions, with observations on the effects of intravenously administered glycine, *J. Clin. Investigation* **27**: 655–664, 1948.

The glycine and total a-amino N levels were studied in several pathological conditions, including a group of endocrine diseases. All glycine values were low in a hypermetabolic patient with a myopathy simulating myasthenia gravis. Elevated values, persisting for at least one month after ablation of the hypophysis, were observed in an acromegalic patient. Blood amino N was normal in the hypermetabolic subjects tested Glycine showed a tendency to elevation in 5 cases of hypometabolism; in only one, a cretin, was the a-amino N also increased. Plasma amino N, originally low in a patient with hypometabolism and nutritional hypoproteinemia, rose steadily, while plasma glycine values increased suddenly from low normal and remained elevated. In one patient with hypothyroidism and in one with acromegaly and hypermetabolism, the glycine tolerance test showed very high plasma and red cell glycine following injection, with an abnormally slow decline; high fasting blood glycine was also noted in these two subjects. A marked rise in plasma glycine after injection, but with an essentially normal subsequent decline, occurred in one patient with hypometabolism and nutritional hypoproteinemia. Low normal plasma glycine was demonstrated in two insulin-treated diabetics, and elevated whole blood and red cell glycine in a case of Addison's disease with scleroderma. *T.H.McG.*

FABRYHART, M., and PACELLA, B. L.: Association of spontaneous hypocalcemia and electrocerebral dysfunction, *Arch. Int. Med.* **81**: 184–202, 1948.

Eight patients presenting symptoms usually observed in psychoneurosis, spontaneous hypoglycemia or hypocalcemia, were studied. Oral glucose tolerance tests, serum calcium determinations, and electroencephalograms were done. The authors stressed the similarity of symptoms in all three conditions. A direct correlation between concentration of glucose in the blood and clinical symptoms was not found, and in the opinion of the authors an abnormally low curve for glucose tolerance is an important and sufficient diagnostic criterion when the clinical picture is present. The electroencephalographic changes consisted for the most part of slow type alpha rhythm and random 6 to 7 cycles per sec-

ond potentials. These changes were considered to reflect a decreased threshold for the development of epileptiform clinical reactions, and not as indicative of epilepsy or a convulsive disorder. Treatment consists of a maintenance diet high in protein with supplementary feedings, phenobarbital and belladonna. Calcium salts were used orally and parenterally in those patients who had associated hypoglycemia.—*C.D.D.*

GALLI MAININI, C.: Pregnancy test using the male batrachia, *J.A.M.A.* **138:** 121 (Sept. 11) 1948.

The author has now thoroughly tested the method he described in 1947 which makes use of the male toad for the assay of chorionic gonadotropin. In his hands the test is remarkably simple and reliable. The injection of 10 cc. of pregnancy urine into the dorsal lymph sac of the male toad causes the appearance of spermatozoa in the urine within one to three hours. No preparation of the urine is required. The results are read by the direct examination under the microscope of a few drops of urine removed from the cloaca. Two thousand and thirty tests were done. In the first to sixth months of pregnancy 99% of urines gave a positive result, in the last trimester 92% did. No false positive test occurred in 623 assays of urine from a variety of nonpregnant cases.—*A.P.F.*

GOLDZIEHER, JOSEPH W.: A new colorimetric method for the determination of pregnandiol, *J. Lab. & Clin. Med.* **33:** 251–253 (Feb.) 1948.

The author describes a colorimetric method for determining pregnandiol which is as sensitive as the sulfuric acid method and yet does not develop adventitious color. The method is based on the interaction of pregnandiol with acetyl chloride and zinc chloride in glacial acetic acid solution. The color obtained is stable and at room temperature, it remains constant for at least two and a half hours. With the use of a standard, containing 0.5 mg. or pregnandiol, the method was found to be accurate within ±4 per cent.—*T.H.McG.*

LEVIN, E.; KIRSNER, J. B., and PALMER, W. L.: Preliminary observations on histamine and insulin stimulated gastric secretion during the injection of an enterogastrone concentrate in man, *Gastroenterology* **10:** 274–280, 1948.

The effect of moderately large quantities of an enterogastrone concentrate upon the gastric secretory response to histamine and to insulin was studied in 15 patients with peptic ulcer. Intramuscular injection of 1000 mg. of the concentrate was followed in one of three patients by a decrease in the gastric secretory response to a single standard dose of histamine; in the one patient studied, the maximum free acidity was not affected by the administration of 3000 mg. of enterogastrone. In seven patients, intramuscular administration of 400 to 2000 mg. of enterogastrone did not alter the gastric secretory response to the repeated injection of small quantities of histamine. Insulin-stimulated gastric secretion in three patients was not altered by intramuscular injection of 1000 mg. of enterogastrone; in one, it was possibly delayed by 2000 mg. and may have been suppressed by 3000 mg. in one. Further observations with more potent preparations in a larger series of cases will be necessary before definite conclusions can be drawn from the last two experiments.—*T.H.McG.*

MCHENRY, E. W.; SEMMONS, E. M.; PEARSE, R., and MEYER, E. G.: Ob-

servations on the ketosteroid content of urine from patients with prostatic carcinoma and adenoma, *Cancer Research* **7**: 534–536, 1947.

Determination by the method of Holtorff and Koch of 17-ketosteroids in 200 24-hour specimens of urine from 32 cases of prostatic carcinoma and 39 cases of benign prostatic adenoma revealed no characteristic alteration of androgen excretion in the prostatic carcinoma subjects. The values were characteristically low as would be expected for the age group tested. There was a definite correlation between specific gravity and total urinary volume suggesting some relationship between renal function and ketosteroid excretion.—*R.H.*

MERCHANTE, FERMIN RAUL: Pregnancy test with the reaction of Galli Mainini, *Semana méd.* **55**: 49–53, 1948.

In this test the urine of the patient is injected into the dorsal lymph sac of the male toad and the appearance of spermatozoa is observed in the urine collected from the bladder. Two toads are used per test and the observation is carried out over 3 to 24 hours although a positive reaction may be observed as early as after 100 minutes. A maximum of 10 cc. of urine is used. In 266 tests correct negative results were recorded in 100 per cent, and correct positive results in 98 per cent of the cases.—*A.E.M.*

PINCUS, J. B.; NATELSON, S., and LUGOVOY, J. K.: Response of citric acid levels to oral administration of glucose. II. Abnormalities observed in the diabetic and convulsive state, *J. Clin. Investigation* **27**: 450–453, 1948.

Part I of this investigation demonstrated *in vivo* in man that the normal response to active carbohydrate metabolism, as in the postabsorptive period for glucose or after injection of insulin, was a lowering of blood citric acid levels. Most of the diabetics studied in this investigation showed no apparent deviation from the normal citric acid level response curve when glucose was administered orally. However, certain diabetic patients with neurologic symptoms who were difficult to control with insulin therapy showed abnormalities in their citric acid response by a rapidly rising level, or by a sharp rise for the first hour of the test period followed by a lowering to the minimum level.—*T.H.McG.*

STUART, HAROLD C.: Physical growth during adolescence, *Am. J. Dis. Child.* **74**: 495–502 (Oct.) 1947.

The author divides the progress of growth from conception to full maturity into 3 major phases: the first and last being characterized by cycles of acceleration followed by deceleration in growth rates, and both accompanied by striking developmental changes. The middle phase is one of relatively steady, moderate progress in both growth and maturation. The last of these three phases is rather loosely called adolescence and preferably called pubescence which is separated from childhood by the preparatory or transitional stage, prepubescence, and from full maturity by a terminal stage, postpubescence.

During prepubescence the rate of body growth begins to accelerate, the sex organs grow more rapidly and certain endocrine glands increase their activity. However, much of the growth of the sex organs takes place during the postpubescent years, after the person has attained approximate adult size and after he appears to have reached ma-

turity in most other respects. The gradual transition from one stage to another and the great individual variability in respect to age make it impossible to delimit precisely the early and late stages of adolescent development in terms of chronologic age, but roughly each stage may be thought of as lasting 2 to 3 years in most persons.

Primary attention in this discussion is devoted to the changes with growth, which are characteristic of the period referred to as pubescence. The principal characteristics of the pubescent growth of the skeleton, including the muscles and the overlying soft tissues are listed and a table showing the common, or characteristic, differences between early and late-maturing persons is presented.—*E.C.R.*

SWANK, R. L., and BERGNER, G. E.: A study of the human myogram. A study of normals, and of patients with Addison's disease, thyrotoxicosis and progressive muscular atrophy, *J. Clin. Investigation* **27**: 24–33 (Jan.) 1948.

A method of myography commonly used in animals was employed in a group of human subjects to record alterations in muscle function. Slight changes in the myogram, correlated with fatigue, were observed in normal subjects. An early dip in the myogram occurred in patients with Addison's disease who exhibited marked weakness. Adequate treatment of these patients with desoxycorticosterone was followed by reversal of these changes toward normal. In the patients with Addison's disease and in two with thyrotoxic myopathy, an absence of potentiation of the muscular contractions normally present during repeated stimulation, was observed. Severe and generalized weakness accompanied this alteration in the myogram, apparently a manifestation of the abnormal metabolic state in the muscles of patients with Addison's disease. Neither hypoxemia nor hypoglycemia of a severe grade per se produced any altered responses in types of tests for muscular function which were here employed. Marked variation in the height of muscular contraction was noted in patients with progressive muscular atrophy.—*T.H.McG.*

ULLMANN, T. D., and SCHORR, S.: Renal dwarfism with hyperparathyroidism in a case of congenital malformation of the kidneys, *Ann. Int. Med.* **29**: 715–730, 1948.

A case of renal dwarfism in a 14-year-old girl, characterized by stunted growth (without manifestations of rickets), infantilism, bilateral congenital dilatation of the renal pelvis and ureters with atrophy of the renal parenchyma and interstitial nephritis, parathyroid hypertrophy and slight osteoporosis is presented. The congenital nature of the kidney disorder, the retardation of growth since early infancy and the presence of similar kidney disorders and subnormal stature in two other female members of the same family are thought to justify an application of the continental theory of "multiple congenital malformations" to the early nonuremic phase of this case. The Anglo-American theory, which maintains a causal relationship between renal insufficiency and skeletal involvement, is invoked to explain only the late manifestations of the patient's disease.—*J.M.*

WYATT, J.: Testosterone propionate in inoperable carcinoma, *J. Obst. & Gynaec. Brit. Emp.* **55**: 53–54, 1948.

A case of squamous celled carcinoma of the uterus in a woman aged 57 years. She was

given 35,000 mg. of testosterone propionate over a two-year period with apparent prolongation of life in comfort.—*R.A.C.*

ZONDEK, B., and BRZEZINSKI, A.: Inactivation of oestrogenic hormone by women with vitamin B deficiency, *J. Obst. & Gynaec. Brit. Emp.* **55**: 273–280, 1948.

Fourteen cases with marked evidence of vitamin B-complex deficiency were studied. No change in estrogen inactivation was found and estrogen titers in blood and urine were normal as well as vaginal smears and endometrial biopsies. It was concluded that the vitamin was not an essential factor in the estrogen-inactivating mechanism.—*R.A.C.*

ZONDEK, B.; SULMAN, F., and BLACK, R.: Hormonal test for fetal death in disturbed pregnancy, *J.A.M.A.* **136**: 965 (Apr. 10) 1948.

Urinary gonadotropin is titrated by the rat ovary hyperemia test described by the authors in 1945. The HU (hyperemia unit) is established for each strain of rat by correlation with estrus units. The technique of the test is reviewed. In disturbed pregnancy a titration is made on four rats injected with 4, 2, 1, and 0,2 cc. of urine which corresponds to titers of 250, 500, 1000 and 5000 HU per liter. Less than 1000 HU indicates probable, and less than 500, certain fetal death in the first two trimesters. During the peak of gonadotropin excretion, between the fortieth and eightieth days after implantation, the normal excretion is about 200,000 HU per liter. A level of 5000 units at this time is consistent with fetal death. Repetition of the test after a week to determine whether the titer is rising or falling assists in predicting the outcome of the pregnancy. Five hundred cases of disturbed pregnancy were studied.—*A.P.F.*